Hindawi Publishing Corporation
Advances in Pharmacological Sciences
Volume 2011, Article ID 435132, 7 pages
doi:10.1155/2011/435132

Review Article

The Role of Uridine Adenosine Tetraphosphate in the Vascular System

Takayuki Matsumoto,[1,2] Rita C. Tostes,[3] and R. Clinton Webb[1]

[1] *Department of Physiology, Georgia Health Sciences University, 1120 Fifteenth Street, CA-3135, Augusta, GA 30912-3000, USA*
[2] *Department of Physiology and Morphology, Institute of Medicinal Chemistry, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan*
[3] *Department of Pharmacology, School of Medicine of Ribeirao Preto, University of Sao Paulo, 14049-900 Sao Paulo, SP, Brazil*

Correspondence should be addressed to Takayuki Matsumoto, t-matsu@hoshi.ac.jp

Received 9 August 2011; Accepted 21 September 2011

Academic Editor: Masahiro Oike

The endothelium plays a pivotal role in vascular homeostasis, and endothelial dysfunction is a major feature of cardiovascular diseases, such as arterial hypertension, atherosclerosis, and diabetes. Recently, uridine adenosine tetraphosphate (Up_4A) has been identified as a novel and potent endothelium-derived contracting factor (EDCF). Up_4A structurally contains both purine and pyrimidine moieties, which activate purinergic receptors. There is an accumulating body of evidence to show that Up_4A modulates vascular function by actions on endothelial and smooth muscle cells. In this paper, we discuss the effects of Up_4A on vascular function and a potential role for Up_4A in cardiovascular diseases.

1. Introduction

A healthy endothelium expresses and releases various molecules, which aid to maintain vascular structure and homeostasis [1, 2]. Endothelial cells actively regulate basal vascular tone and vascular reactivity in physiological and pathophysiological conditions, by responding to mechanical forces (e.g., shear stress) and neurohumoral mediators with the release of a variety of relaxing factors [endothelium-derived relaxing factors (EDRFs)] or contracting factors [endothelium-derived contracting factors (EDCFs)] [3–5]. Endothelial dysfunction plays a key role in the initiation and development of both macro- and microangiopathy in patients with arterial hypertension, inflammatory-associated diseases (atherosclerosis), hypercholesterolemia, stroke, diabetes, as well as in animal models of these diseases [4–12]. The mechanisms that regulate the balance between EDRFs and EDCFs are important for vascular health. Mechanisms that increase EDRFs and/or decrease the release and/or bioavailability of EDCFs are promising drug targets to alleviate the damage caused by endothelial dysfunction. So far, several factors are known as EDCFs such as endothelin-1, angiotensin II, vasoconstrictor prostanoids, and reactive oxygen species [4, 5, 13].

The dinucleotide uridine adenosine tetraphosphate (Up_4A) (Figure 1) was identified by Jankowski et al. [14] as a novel potent EDCF. Up_4A was isolated from the supernatant of stimulated human endothelium and was identified by mass spectrometry. Up_4A is released from the endothelium in response to acetylcholine (ACh), the calcium ionophore (A23187), endothelin-1, adenosine triphosphate (ATP), uridine triphosphate (UTP), and mechanical stress. Therefore, Up_4A can contribute to vascular regulation as an endothelium-derived factor [14]. Up_4A plasma concentrations detected in healthy subjects are high enough to cause vasoconstriction [14]. Moreover, Up_4A is the first dinucleotide found in living organisms that contains both purine and pyrimidine moieties (Figure 1).

Purinergic signaling is important not only in short-term regulation of vascular tone but also in long-term regulation of vascular remodeling (i.e., vascular cell proliferation, migration, and death) [15–21]. Moreover, dinucleotides containing two purine moieties are known, and their role in vasomotor regulation is increasingly recognized [20, 22, 23].

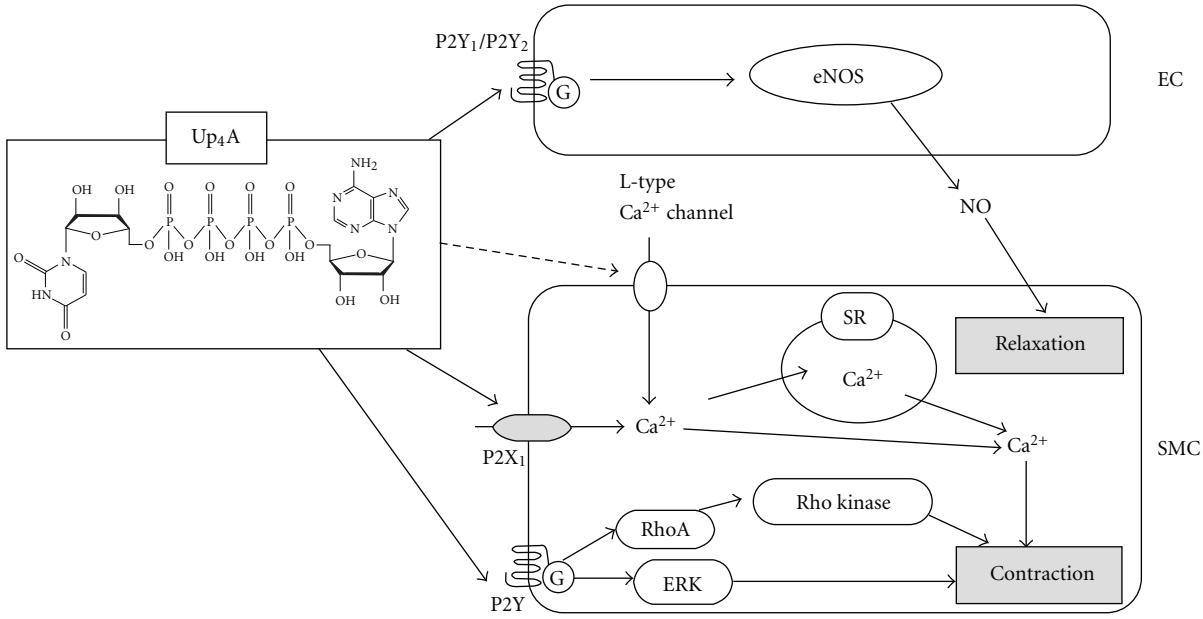

Figure 1: Up_4A and vascular tone. Details are shown in the text. Up_4A may directly or indirectly activate L-type Ca^{2+} channel. NO: nitric oxide; eNOS: endothelial nitric oxide synthase; EC: endothelial cell; SMC: smooth muscle cell; SR: sarcoplasmic reticulum; ERK: extracellular signal regulated kinase.

However, the vasoactivity of Up_4A may differ from those of dinucleotides exclusively containing purines [20, 24]. Therefore, Up_4A can play a functional role in the vascular system both under physiological and pathophysiological conditions.

This paper focuses on the effects of Up_4A on vascular tone and its putative role on vascular function.

2. Up_4A and Vascular Tone under Physiological Conditions

Several reports demonstrated that Up_4A modulates vasomotor activity in vessels from nondisease animal models using both *in vitro* (i.e., perfusion or myograph system) and *in vivo* techniques (Table 1, Figure 1). Since Up_4A possesses both purine and pyrimidine moiety, these studies mainly focus on the relationship between Up_4A and purinoceptor signaling.

Purinoceptors have been classified into two subtypes (namely, P1 receptors (or adenosine receptors) and P2 receptors) based on their molecular cloning and pharmacological properties [25–28]. Adenosine and its phosphates, ATP and ADP, have been identified as the endogenous ligand for P1 and P2 receptors, respectively. Four subtypes of metabotropic P1 receptors have been cloned and named A1, A2A, A2B, and A3 [25, 27]. The P2 receptors exist in two major families: ionotropic (P2X receptors) and metabotropic (P2Y receptors) [26–30]. Currently, there are at least 7 cloned P2X receptors and at least 8 cloned P2Y receptors [15–18, 21, 25–30]. P2X receptors are mainly activated by ATP and its analogs, whereas P2Y receptors can be activated by ATP, UTP, and UDP, depending on the subtypes of P2Y receptors involved [15–18, 21, 25–30]. Most of these receptors are capable of mediating responses to several nucleotides, resulting in multiple receptors having overlapping ligand preferences. In addition, distribution of these receptors varies among different tissues [15–18, 21, 25–30]. Therefore, purinergic signaling is complicated. In this section, we will describe reports suggesting that Up_4A affects vascular tone and discuss the relevant mechanisms involved in Up_4A responses.

2.1. Aorta (Rat). Linder et al. [31] characterized the effect of Up_4A in thoracic aorta from rats using isometric tension recording. In intact aortic rings precontracted with phenylephrine, Up_4A treatment led to a modest endothelium-dependent relaxation. On the other hand, under basal conditions, Up_4A induced a concentration-dependent contraction. This contraction was potentiated by endothelium denudation or nitric oxide synthase (NOS) inhibition suggesting that EDRF (mainly NO) constitutively suppresses Up_4A-induced contraction in thoracic aorta. Linder et al. [31] further found that Up_4A-induced contraction was suppressed by P1 (8-PST [32]) or P2X (NF279 [33]) receptor antagonists, L-type Ca^{2+} channel blockade (nifedipine [34]), and Rho-kinase inhibition (Y27632 [35]). These results suggested that Up_4A-induced contraction is modulated by NO, mediated by P1 and P2X receptor activation, and involves L-type Ca^{2+} channels and Rho-kinase activation in smooth muscle cells. Moreover, Up_4A-induced contraction was attenuated by a membrane permeable superoxide scavenger (tempol) and by an NADPH oxidase inhibitor (apocynin) suggesting that superoxide generation affects Up_4A-induced contractile responses [31].

2.2. Pulmonary Artery (Rat). Gui et al. [36] characterized the effect of Up_4A in pulmonary artery from rats using isometric

Table 1: Up_4A and vascular reactivity.

Artery/tissue	Animal	Response	Putative receptor	Signaling	Reference
Thoracic aorta	Rat	Contraction Relaxation	P1, P2X	L-type Ca^{2+} channel Rho kinase Superoxide NO (endothelium-dependent)	[31]
Pulmonary artery	Rat	Contraction	P2Y	Ca^{2+} (extracellular and intracellular stores)	[36]
Thoracic aorta	Mouse	Contraction Relaxation			[41]
Perfused kidney	Rat	Contraction Relaxation	$P2X_1$, $P2Y_2$, $P2Y_4$ $P2Y_1$, $P2Y_2$	NO	[14] [37] [37]
Perfused afferent arterioles	Mouse	Contraction			[38]

NO: nitric oxide. Details are shown in the text.

tension recording and investigated the signaling mechanisms related to Up_4A responses. Up_4A induced concentration-dependent contraction of isolated rat pulmonary arteries. Up_4A was as potent as UTP and UDP in endothelium-denuded arteries, while much more effective than UTP and UDP in endothelium-intact preparations [36]. Up_4A -induced contraction was blocked by suramin, but not by P2X receptor antagonist (Ip_5I) or desensitization of P2X receptors with α,β-methylene-ATP [36]. Up_4A -induced contraction was inhibited by pretreatment with an inhibitor of Ca^{2+} release from sarcoplasmic reticulum (thapsigargin), a Ca^{2+} channel blocker (nitrendipine) and a Ca^{2+} chelator (EGTA), but unaffected by a Rho-kinase inhibitor (H-1152) [36]. Moreover, unlike ATP and UTP, Up_4A does not induce vasodilation of endothelium-intact preparations contracted with phenylephrine [36]. These results suggest that Up_4A is a potent vasoconstrictor, but not a vasodilator in the rat pulmonary artery, and such contraction is mainly via a suramin-sensitive P2Y receptor. The contractile effect of Up_4A involves the entry of extracellular Ca^{2+} and release of Ca^{2+} from intracellular stores but not Ca^{2+} sensitization due to the activation of RhoA/Rho kinase pathway in vascular smooth muscle cells. Therefore, Up_4A potentially plays an important role in the regulation of pulmonary vascular tone.

2.3. Renal Artery (Rat and Mouse). Jankowski et al. [14] observed that in rat isolated perfused kidney, Up_4A stimulated vasoconstriction mainly via $P2X_1$ receptors and probably also via $P2Y_2$ and $P2Y_4$ receptors. Very recently, findings from this same group indicate that in the rat perfused kidney, in addition to smooth muscle $P2X_1$ receptor-mediated vasoconstriction, Up_4A showed concentration-dependent $P2Y_2$ receptor-mediated, long-lasting vasoconstriction [37]. Moreover, they demonstrated that Up_4A-induced vasoconstriction was followed by vasodilation mediated by $P2Y_1$ and $P2Y_2$ receptor activation on endothelial cells leading to the release of NO [37].

In mouse vessels, Up_4A acts as a strong vasoconstrictive mediator on afferent arterioles, but has no significant effect on the tone of efferent arterioles [38]. The selective preglomerular vasoconstrictor activity of Up_4A may be due to the lack of $P2X_1$ receptors, which are the main target of Up_4A, in postglomerular arterioles [39]. Therefore, it may be assumed that Up_4A contributes to the regulation of glomerular perfusion, intraglomerular pressure, and glomerular filtration rate. Moreover, Up_4A was synthesized/secreted not only by the endothelium but also by renal tubular cells. Stimulation of tubule cells with oleoyl-2-acetyl-sn-glycerol (OAG, protein kinase C activator) increases the release rate of Up_4A from tubule cells approximately 10-fold [38]. The release of Up_4A from renal tubular cells may affect renal perfusion. Up_4A release may further contribute to renal vascular autoregulation mechanisms [19, 40].

These results suggest that Up_4A may play an important role in renal haemodynamics and blood pressure regulation.

2.4. Aorta (Mouse). Hansen et al. [41] characterized the effects of Up_4A in aorta from mice using isometric tension recording and *in vivo* arterial pressure measurements in conscious mice and rats (see below). Up_4A has both relaxing and contracting effects depending on the Up_4A concentration, the presence of precontraction, and the mode of stimulation (namely, single versus cumulative dose/concentrations). Up_4A produced contraction in mouse aorta. In rings precontracted with phenylephrine, Up_4A induced relaxation. A pronounced transient contraction was observed when 10^{-5} M Up_4A was added as a bolus, while vasodilation was predominant when Up_4A was added cumulatively. The contraction induced by low concentrations of Up_4A was abolished by a cyclooxygenase inhibitor (indomethacin), suggesting that Up_4A-induced contraction may be attributable to cyclooxygenase metabolites. Therefore, Up_4A can evoke both relaxation and contraction in mouse aorta as well as rat aorta [31].

2.5. Up_4A Affects Arterial Blood Pressure In Vivo (Rat and Mouse). Jankowski et al. [14] investigated the effects of Up_4A on mean arterial pressure of rats. Both noradrenaline and Up_4A increased mean arterial pressure when injected intra-aortically in the anesthetized rat. Although noradrenaline evoked a sharp, short-lasting increase in arterial blood pressure, the same amount of Up_4A showed a more prolonged effect on arterial blood pressure.

Hansen et al. [41] determined the effects of Up_4A on mean arterial pressure in conscious mice and rats. Intravenous infusion of increasing doses of Up_4A to unrestrained mice and to conscious, trained rats caused a decrease in mean arterial pressure at higher rates of administration concomitant with a marked antinatriuretic effect. The discrepancy between the two studies may be explained by differences between the methodologies (namely, unconscious versus conscious) and by differences in the administration of Up_4A (namely, single dose versus step-up doses). Future experiments need to be performed to address this question.

Table 1 and Figure 1 summarize Up_4A effects on various arteries from different species.

3. Up_4A and Pathophysiological States

There is evidence that Up_4A might have implications in the pathogenesis of human arterial hypertension. Jankowski et al. [42] demonstrated that the plasma concentrations of Up_4A are increased in juvenile hypertensive humans compared with normotensive subjects. Up_4A concentration significantly correlates with the left ventricular mass and intima/media wall thickness in the hypertensive patients [42]. Therefore, Up_4A may have an association with hypertension and hypertension-related vascular abnormalities.

As mentioned above, so far, the studies of Up_4A-mediated responses have been carried out only in normal animals, and there is no study to indicate the vascular effects of Up_4A under pathophysiological conditions, such as arterial hypertension. Since the vascular responsiveness to Up_4A in hypertensive states remains unexplored/unknown, we [43] recently addressed this issue using deoxycorticosterone acetate-salt (DOCA-salt) rats, a well-known salt-dependent experimental model of arterial hypertension [44–47]. Using isometric tension recording (myograph), we observed that Up_4A produced concentration-dependent contractions in segments of renal and pulmonary arteries at basal resting tension [43]. In DOCA-salt rats [versus its control uninephrectomized (Uni) rats], Up_4A-induced contraction was similar in pulmonary artery and greater in renal artery [43]. Up_4A-induced contraction in renal artery from both DOCA-salt and control groups was inhibited by a nonselective P2 receptor antagonist (suramin) but not by a P2X receptor antagonist (Ip_5I). Furthermore, selective $P2Y_2$ agonist-(2-Thio-UTP-), $P2Y_2$/$P2Y_4$ agonist-(UTPγS-), and $P2Y_6$ agonist-(MRS2693-) induced contractions were all increased in renal artery from DOCA-salt rats. Renal arterial protein expression of $P2Y_2$, $P2Y_4$, and $P2Y_6$ receptors was similar between the two groups. The extracellular signal regulated kinase (ERK) pathway plays important roles in the regulation of vascular tone [46, 48–50], and it has been demonstrated that P2Y receptor activation can induce ERK pathway activation [18, 28, 51]. In DOCA-salt renal artery, the enhanced Up_4A-induced contraction was reduced by an ERK pathway inhibitor (PD98059), and ERK activation stimulated by Up_4A was enhanced in renal artery from DOCA-salt rats. Enhanced P2Y receptor signaling and activation of the ERK pathway represent likely mechanisms mediating the augmented Up_4A-induced contraction in renal artery from DOCA-salt hypertensive rats. Moreover, we recently observed that, in DOCA-salt rats (versus Uni rats), Up_4A-induced contraction was increased in basilar and femoral arteries, was decreased in small mesenteric artery, and was unchanged in thoracic aorta [52]. These results suggest that Up_4A-induced contraction is heterogeneously affected among several vascular beds in DOCA-salt hypertensive rats. These results indicate that abnormal Up_4A-induced contraction may be associated with the vascular dysfunction seen in hypertension.

Jankowski et al. [42] also found that Up_4A could lead to proliferation of human vascular smooth muscle cells (VSMCs). This cell-cycle-dependent process involves stimulation of S phase entry, and is due to the activation of P2Y receptor rather than P2X receptor. Very recently, Gui et al. [53] also suggested that Up_4A stimulated proliferation of VSMCs via activation of P2Y receptors and the PI3-kinase/Akt and mitogen-activated protein kinase (MAPK) pathways. Since increased proliferation of VSMCs reflects not only on intima/media wall thickness but also on atherogenesis [54–57], Up_4A may play a potential role in the development of atherosclerosis.

Schuchardt et al. [58] investigated the influence of Up_4A on formation of monocyte chemoattractant protein-1 (MCP-1), which is an important early component of the inflammatory response in atherosclerosis and induced by oxidative stress [56, 59–61]. The authors also characterized the underlying signaling transduction mechanisms in rat VSMCs. Up_4A induced MCP-1 expression and secretion in VSMCs through the activation of $P2Y_2$ receptor in a concentration-dependent manner. MCP-1 formation depended on generation of ROS. Up_4A-induced MCP-1 formation was suppressed by NAD(P)H oxidase inhibitors (apocynin and diphenyl-iodonium) and by siRNA against NOX1 (a component of NAD(P)H oxidase [62–64]). Moreover, Up_4A stimulated Rac1 activation and $p47^{phox}$ translocation from cytosol to the plasma membrane (these processes are required for assembling and activation of NOX). The activation of MAPKs (i.e., ERK1/2 and p38 MAPK) is essential for Up_4A-mediated intracellular signal transduction [58]. These results clearly demonstrated that Up_4A induces NOX1-dependent ROS production, which further stimulates MCP-1 formation through MAPK phosphorylation in VSMCs. This process requires the activation of $P2Y_2$ receptor. Thus, Up_4A is not only a potent EDCF but also a potent inducer of proinflammatory response in the vascular wall.

Moreover, Up_4A has a stimulatory effect on the oxidative burst response (ROS production) of nonstimulated and *N*-formyl-methionine-leucine-phenylalanine-(fMLP-) activated monocytes as well as after phorbol 12-myristate

13-acetate (PMA) stimulation of both monocytes and lymphocytes [65]. Chronic inflammation in chronic kidney disease or atherosclerosis is associated with oxidative stress, and leukocytes are an important source of ROS [56, 57, 66]. Up_4A potentially has impact on the initiation and progression of vascular inflammatory diseases and may represent a linking between blood pressure regulation and atherosclerosis.

4. Conclusions

The present work reviews reported studies on the effects of Up_4A on vascular function in physiological and pathophysiological states. Although Up_4A definitely has an important role in vascular function, some questions currently remain unresolved. For instance, what are the mechanisms of synthesis and catabolism of Up_4A? To what extent are there regionally differences in Up_4A kinetics? Are there mechanisms modified in vessels under physiological and pathophysiological states? How and to what extent do Up_4A receptor(s) interact with Up_4A putative degradation forms (e.g., mononucleotides and nucleotides) in the vascular system? How do the vascular actions of Up_4A change during aging? Are there sex differences in the response to the dinucleotide? Since ion channels (e.g., P2X receptor) and G protein-coupled receptor (e.g., P2Y receptor and adenosine receptor) participate in multiprotein complexes with signaling molecules and other receptors (dimerized receptor or unknown Up_4A specific receptor) should also be investigated in physiological and pathophysiological states. A comprehension of the vascular effects of Up_4A in other cardiovascular diseases, such as atherosclerosis, diabetes, and stroke should also be encouraged.

A better understanding of the role of Up_4A on vascular function and the regulation of Up_4A signaling may provide new insights into the mechanisms responsible for cardiovascular diseases and ultimately lead to novel therapeutic strategies with the potential to improve of prognosis of cardiovascular diseases.

Disclosures

No cinflicted of interests, financial or otherwise, are declared by the authors.

Acknowledgments

This work was supported in part by the National Institutes of Health (Grants R01 HL-071138 and R01 DK-083685) and by the Naito Foundation Japan.

References

[1] U. Landmesser, B. Hornig, and H. Drexler, "Endothelial function: a critical determinant in atherosclerosis?" *Circulation*, vol. 109, no. 21, supplement 1, pp. II27–II33, 2004.

[2] M. Félétou and P. M. Vanhoutte, "Endothelial dysfunction: a multifaceted disorder (The Wiggers Award Lecture)," *American Journal of Physiology*, vol. 291, no. 3, pp. H985–H1002, 2006.

[3] R. O. Cannon III, "Role of nitric oxide in cardiovascular disease: focus on the endothelium," *Clinical Chemistry*, vol. 44, no. 8, pp. 1809–1819, 1998.

[4] P. M. Vanhoutte, M. Feletou, and S. Taddei, "Endothelium-dependent contractions in hypertension," *British Journal of Pharmacology*, vol. 144, no. 4, pp. 449–458, 2005.

[5] E. H. Tang and P. M. Vanhoutte, "Endothelial dysfunction: a strategic target in the treatment of hypertension?" *Pflugers Archiv European Journal of Physiology*, vol. 459, no. 6, pp. 995–1004, 2010.

[6] M. Barton, "Obesity and aging: determinants of endothelial cell dysfunction and atherosclerosis," *Pflugers Archiv European Journal of Physiology*, vol. 460, no. 5, pp. 825–837, 2010.

[7] T. Matsumoto, T. Kobayashi, and K. Kamata, "Relationships among ET-1, PPARγ, oxidative stress and endothelial dysfunction in diabetic animals," *Journal of Smooth Muscle Research*, vol. 44, no. 2, pp. 41–55, 2008.

[8] A. Virdis, L. Ghiadoni, and S. Taddei, "Human endothelial dysfunction: EDCFs," *Pflugers Archiv*, vol. 459, no. 6, pp. 1015–1023, 2010.

[9] D. Versari, E. Daghini, A. Virdis, L. Ghiadoni, and S. Taddei, "Endothelium-dependent contractions and endothelial dysfunction in human hypertension," *British Journal of Pharmacology*, vol. 157, no. 4, pp. 527–536, 2009.

[10] P. M. Vanhoutte, H. Shimokawa, E. H. Tang, and M. Feletou, "Endothelial dysfunction and vascular disease," *Acta Physiologica*, vol. 196, no. 2, pp. 193–222, 2009.

[11] E. L. Schiffrin, "A critical review of the role of endothelial factors in the pathogenesis of hypertension," *Journal of Cardiovascular Pharmacology*, vol. 38, supplement 2, pp. S3–S6, 2002.

[12] Q. Chen, E. E. Kim, K. Elio et al., "The Role of tetrahydrobiopterin and dihydrobiopterin in ischemia/reperfusion injury when given at reperfusion," *Advances in Pharmacological Sciences*, vol. 2010, Article ID 963914, 2010.

[13] R. C. Tostes, Z. B. Fortes, G. E. Callera et al., "Endothelin, sex and hypertension," *Clinical Science*, vol. 114, no. 1-2, pp. 85–97, 2008.

[14] V. Jankowski, M. Tölle, R. Vanholder et al., "Uridine adenosine tetraphosphate: a novel endothelium-derived vasoconstrictive factor," *Nature Medicine*, vol. 11, no. 2, pp. 223–227, 2005.

[15] G. Burnstock, "Purinergic signaling and vascular cell proliferation and death," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 22, no. 3, pp. 364–373, 2002.

[16] G. Burnstock, "Dual control of vascular tone and remodelling by ATP released from nerves and endothelial cells," *Pharmacological Reports*, vol. 60, no. 1, pp. 12–20, 2008.

[17] G. Burnstock, "Purinergic regulation of vascular tone and remodelling," *Autonomic and Autacoid Pharmacology*, vol. 29, no. 3, pp. 63–72, 2009.

[18] L. Erb, Z. Liao, C. I. Seye, and G. A. Weisman, "P2 receptors: intracellular signaling," *Pflugers Archiv*, vol. 452, no. 5, pp. 552–562, 2006.

[19] Z. Guan, D. A. Osmond, and E. W. Inscho, "P2X receptors as regulators of the renal microvasculature," *Trends in Pharmacological Sciences*, vol. 28, no. 12, pp. 646–652, 2007.

[20] V. Jankowski, M. van der Giet, H. Mischak, M. Morgan, W. Zidek, and J. Jankowski, "Dinucleoside polyphosphates: strong endogenous agonists of the purinergic system," *British Journal of Pharmacology*, vol. 157, no. 7, pp. 1142–1153, 2009.

[21] D. Erlinge and G. Burnstock, "P2 receptors in cardiovascular regulation and disease," *Purinergic Signalling*, vol. 4, no. 1, pp. 1–20, 2008.

[22] G. Gabriëls, K. H. Rahn, E. Schlatter, and M. Steinmetz, "Mesenteric and renal vascular effects of diadenosine polyphosphates (APnA)," *Cardiovascular Research*, vol. 56, no. 1, pp. 22–32, 2002.

[23] N. A. Flores, B. M. Stavrou, and D. J. Sheridan, "The effects of diadenosine polyphosphates on the cardiovascular system," *Cardiovascular Research*, vol. 42, no. 1, pp. 15–26, 1999.

[24] M. van der Giet, T. Westhoff, O. Cinkilic et al., "The critical role of adenosine and guanosine in the affinity of dinucleoside polyphosphates to P_{2X}-receptors in the isolated perfused rat kidney," *British Journal of Pharmacology*, vol. 132, no. 2, pp. 467–474, 2001.

[25] B. B. Fredholm, A. P. IJzerman, K. A. Jacobson, J. Linden, and C. E. Müller, "International union of basic and clinical pharmacology. LXXXI. Nomenclature and classification of adenosine receptors—an update," *Pharmacological Reviews*, vol. 63, no. 1, pp. 1–34, 2011.

[26] G. Burnstock, "Purine and pyrimidine receptors," *Cellular and Molecular Life Sciences*, vol. 64, no. 12, pp. 1471–1483, 2007.

[27] S. P. H. Alexander, A. Mathie, and J. A. Peters, "Guide to receptors and channels (GRAC), 4th edition," *British Journal of Pharmacology*, vol. 158, supplement 1, p. S1, 2009.

[28] M. P. Abbracchio, G. Burnstock, J. M. Boeynaems et al., "International union of pharmacology LVIII: update on the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy," *Pharmacological Reviews*, vol. 58, no. 3, pp. 281–341, 2006.

[29] I. von Kügelgen, "Pharmacological profiles of cloned mammalian P2Y-receptor subtypes," *Pharmacology & Therapeutics*, vol. 110, no. 3, pp. 415–432, 2006.

[30] A. Surprenant and R. Alan North, "Signaling at purinergic P2X receptors," *Annual Review of Physiology*, vol. 71, pp. 333–359, 2009.

[31] A. E. Linder, M. Tumbri, F. F. Linder, R. C. Webb, and R. Leite, "Uridine adenosine tetraphosphate induces contraction and relaxation in rat aorta," *Vascular Pharmacology*, vol. 48, no. 4–6, pp. 202–207, 2008.

[32] R. F. Bruns, "Adenosine antagonism by purines, pteridines and benzopteridines in human fibroblasts," *Biochemical Pharmacology*, vol. 30, no. 4, pp. 325–333, 1981.

[33] S. Damer, B. Niebel, S. Czeche et al., "NF279: a novel potent and selective antagonist of P2X receptor-mediated responses," *European Journal of Pharmacology*, vol. 350, no. 1, pp. R5–R6, 1998.

[34] A. P. Stork and T. M. Cocks, "Pharmacological reactivity of human epicardial coronary arteries: phasic and tonic responses to vasoconstrictor agents differentiated by nifedipine," *British Journal of Pharmacology*, vol. 113, no. 4, pp. 1093–1098, 1994.

[35] S. Narumiya, T. Ishizaki, and M. Uehata, "Use and properties of ROCK-specific inhibitor Y-27632," *Methods in Enzymology*, vol. 325, pp. 273–284, 2000.

[36] Y. Gui, M. P. Walsh, V. Jankowski, J. Jankowski, and X. L. Zheng, "Up_4A stimulates endothelium-independent contraction of isolated rat pulmonary artery," *American Journal of Physiology*, vol. 294, no. 4, pp. L733–L738, 2008.

[37] M. Tölle, M. Schuchardt, A. Wiedon et al., "Differential effects of uridine adenosine tetraphosphateon purinoceptors in the rat isolated perfused kidney," *British Journal of Pharmacology*, vol. 161, no. 3, pp. 530–540, 2010.

[38] V. Jankowski, A. Patzak, S. Herget-Rosenthal et al., "Uridine adenosine tetraphosphate acts as an autocrine hormone affecting glomerular filtration rate," *Journal of Molecular Medicine*, vol. 86, no. 3, pp. 333–340, 2008.

[39] C. M. Chan, R. J. Unwin, M. Bardini et al., "Localization of $P2X_1$ purinoceptors by autoradiography and immunohistochemistry in rat kidneys," *American Journal of Physiology*, vol. 274, no. 4, pp. F799–F804, 1998.

[40] E. W. Inscho, A. K. Cook, J. D. Imig, C. Vial, and R. J. Evans, "Physiological role for $P2X_1$ receptors in renal microvascular autoregulatory behavior," *The Journal of Clinical Investigation*, vol. 112, no. 12, pp. 1895–1905, 2003.

[41] P. B. Hansen, A. Hristovska, H. Wolff, P. Vanhoutte, B. L. Jensen, and P. Bie, "Uridine adenosine tetraphosphate affects contractility of mouse aorta and decreases blood pressure in conscious rats and mice," *Acta Physiologica*, vol. 200, no. 2, pp. 171–179, 2010.

[42] V. Jankowski, A. A. Meyer, P. Schlattmann et al., "Increased uridine adenosine tetraphosphate concentrations in plasma of juvenile hypertensives," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 27, no. 8, pp. 1776–1781, 2007.

[43] T. Matsumoto, R. C. Tostes, and R. C. Webb, "Uridine adenosine tetraphosphate-induced contraction is increased in renal but not pulmonary arteries from DOCA-salt hypertensive rats," *American Journal of Physiology*, vol. 301, no. 2, pp. H409–H417, 2011.

[44] V. V. Lima, F. R. Giachini, F. S. Carneiro et al., "O-glcnacylation contributes to augmented vascular reactivity induced by endothelin 1," *Hypertension*, vol. 55, no. 1, pp. 180–188, 2010.

[45] V. V. Lima, F. R. Giachini, H. Choi et al., "Impaired vasodilator activity in deoxycorticosterone acetate-salt hypertension is associated with increased protein O-GlcNAcylation," *Hypertension*, vol. 53, no. 2, pp. 166–174, 2009.

[46] F. R. Giachini, J. C. Sullivan, V. V. Lima et al., "Extracellular signal-regulated kinase 1/2 activation, via downregulation of mitogen-activated protein kinase phosphatase 1, mediates sex differences in desoxycorticosterone acetate-salt hypertension vascular reactivity," *Hypertension*, vol. 55, no. 1, pp. 172–179, 2010.

[47] T. Szasz and S. W. Watts, "Uric acid does not affect the acetylcholine-induced relaxation of aorta from normotensive and deoxycorticosterone acetate-salt hypertensive rats," *The Journal of Pharmacology and Experimental Therapeutics*, vol. 333, no. 3, pp. 758–763, 2010.

[48] F. R. Giachini, S. M. Zemse, F. S. Carneiro et al., "Interleukin-10 attenuates vascular responses to endothelin-1 via effects on ERK1/2-dependent pathway," *American Journal of Physiology*, vol. 296, no. 2, pp. H489–H496, 2009.

[49] T. Matsumoto, K. Ishida, N. Nakayama, T. Kobayashi, and K. Kamata, "Involvement of NO and MEK/ERK pathway in enhancement of endothelin-1-induced mesenteric artery contraction in later-stage type 2 diabetic Goto-Kakizaki rat," *American Journal of Physiology*, vol. 296, no. 5, pp. H1388–H1397, 2011.

[50] T. Kobayashi, T. Nogami, K. Taguchi, T. Matsumoto, and K. Kamata, "Diabetic state, high plasma insulin and angiotensin II combine to augment endothelin-1-induced vasoconstriction via ETA receptors and ERK," *British Journal of Pharmacology*, vol. 155, no. 7, pp. 974–983, 2008.

[51] O. Ö. Braun, D. Lu, N. Aroonsakool, and P. A. Insel, "Uridine triphosphate (UTP) induces profibrotic responses in cardiac fibroblasts by activation of P2Y2 receptors," *Journal of*

Molecular and Cellular Cardiology, vol. 49, no. 3, pp. 362–369, 2010.

[52] T. Matsumoto, R. C. Tostes, and R. C. Webb, "Alterations in vasoconstrictor responses to the endothelium-derived contracting factor uridine adenosine tetraphosphate are region specific in DOCA-salt hypertensive rats," *Pharmacological Research*. In press.

[53] Y. Gui, G. He, M. P. Walsh, and X.-L. Zheng, "Signaling mechanisms mediating Up_4A-induced proliferation of human vascular smooth muscle cells," *Journal of Cardiovascular Pharmacology*. In press.

[54] S. W. Rabkin, "The role of interleukin 18 in the pathogenesis of hypertension-induced vascular disease," *Nature Clinical Practice Cardiovascular Medicine*, vol. 6, no. 3, pp. 192–199, 2009.

[55] P. Libby, P. M. Ridker, and G. K. Hansson, "Inflammation in atherosclerosis. From pathophysiology to practice," *Journal of the American College of Cardiology*, vol. 54, no. 23, pp. 2129–2138, 2009.

[56] T. Matsumoto, T. Kobayashi, and K. Kamata, "Role of lysophosphatidylcholine (LPC) in atherosclerosis," *Current Medicinal Chemistry*, vol. 14, no. 30, pp. 3209–3220, 2007.

[57] R. Ross, "Atherosclerosis—an inflammatory disease," *The New England Journal of Medicine*, vol. 340, no. 2, pp. 115–126, 1999.

[58] M. Schuchardt, J. Prüfer, N. Prüfer et al., "The endothelium-derived contracting factor uridine adenosine tetraphosphate induces P2Y2-mediated pro-inflammatory signaling by monocyte chemoattractant protein-1 formation," *Journal of Molecular Medicine*, vol. 89, no. 8, pp. 799–810, 2011.

[59] M. Simionescu, "Implications of early structural-functional changes in the endothelium for vascular disease," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 27, no. 2, pp. 266–274, 2007.

[60] I. F. Charo and R. Taub, "Anti-inflammatory therapeutics for the treatment of atherosclerosis," *Nature Reviews Drug Discovery*, vol. 10, no. 5, pp. 365–376, 2011.

[61] I. F. Charo and R. M. Ransohoff, "The many roles of chemokines and chemokine receptors in inflammation," *The New England Journal of Medicine*, vol. 354, no. 6, pp. 610–621, 2006.

[62] M. Katsuyama, "NOX/NADPH oxidase, the superoxide-generating enzyme: its transcriptional regulation and physiological roles," *Journal of Pharmacological Sciences*, vol. 114, no. 2, pp. 134–146, 2010.

[63] R. M. Touyz and A. M. Briones, "Reactive oxygen species and vascular biology: implications in human hypertension," *Hypertension Research*, vol. 34, no. 1, pp. 5–14, 2011.

[64] G. R. Drummond, S. Selemidis, K. K. Griendling, and C. G. Sobey, "Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets," *Nature Reviews Drug Discovery*, vol. 10, no. 6, pp. 453–471, 2011.

[65] E. Schepers, G. Glorieux, V. Jankowski, A. Dhondt, J. Jankowski, and R. Vanholder, "Dinucleoside polyphosphates: newly detected uraemic compounds with an impact on leucocyte oxidative burst," *Nephrology Dialysis Transplantation*, vol. 25, no. 8, pp. 2636–2644, 2010.

[66] G. Zalba, A. Fortuño, and J. Díez, "Oxidative stress and atherosclerosis in early chronic kidney disease," *Nephrology Dialysis Transplantation*, vol. 21, no. 10, pp. 2686–2690, 2006.