

## Review Article

# The Role of Uridine Adenosine Tetraphosphate in the Vascular System

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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<sub>4</sub>A) has been identified as a novel and potent endothelium-derived contracting factor (EDCF). Up<sub>4</sub>A structurally contains both purine and pyrimidine moieties, which activate purinergic receptors. There is an accumulating body of evidence to show that Up<sub>4</sub>A modulates vascular function by actions on endothelial and smooth muscle cells. In this paper, we discuss the effects of Up<sub>4</sub>A on vascular function and a potential role for Up<sub>4</sub>A 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<sub>4</sub>A) (Figure 1) was identified by Jankowski et al. [14] as a novel potent EDCF. Up<sub>4</sub>A was isolated from the supernatant of stimulated human endothelium and was identified by mass spectrometry. Up<sub>4</sub>A 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<sub>4</sub>A can contribute to vascular regulation as an endothelium-derived factor [14]. Up<sub>4</sub>A plasma concentrations detected in healthy subjects are high enough to cause vasoconstriction [14]. Moreover, Up<sub>4</sub>A 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].

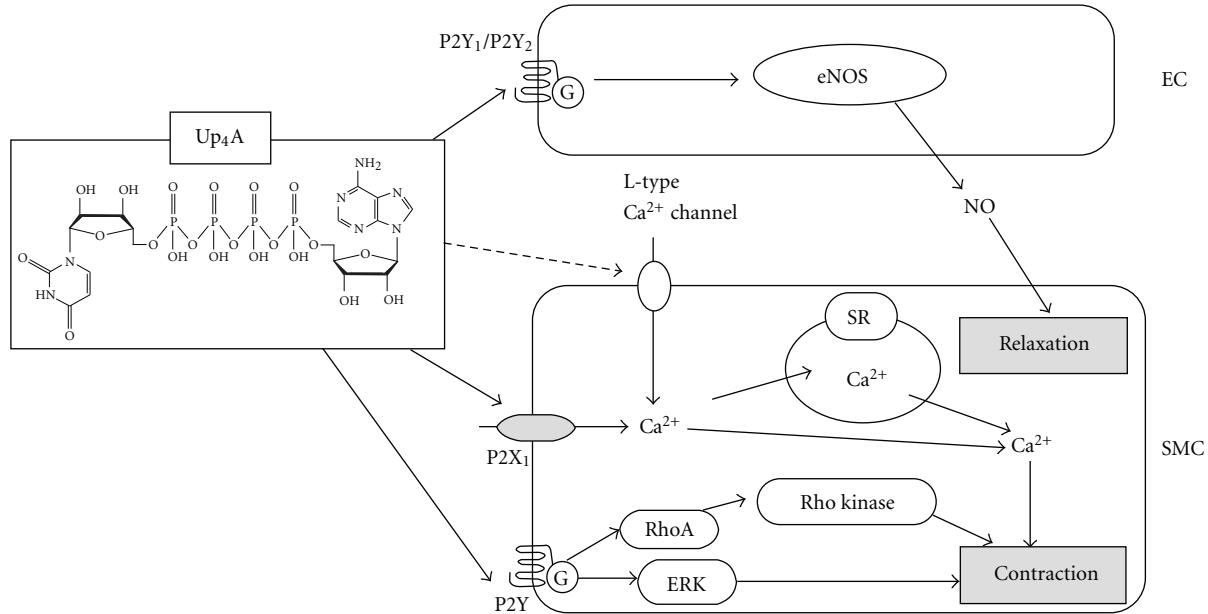


FIGURE 1: Up<sub>4</sub>A and vascular tone. Details are shown in the text. Up<sub>4</sub>A may directly or indirectly activate L-type Ca<sup>2+</sup> channel. NO: nitric oxide; eNOS: endothelial nitric oxide synthase; EC: endothelial cell; SMC: smooth muscle cell; SR: sarcoplasmic reticulum; ERK: extracellular signal regulated kinase.

However, the vasoactivity of Up<sub>4</sub>A may differ from those of dinucleotides exclusively containing purines [20, 24]. Therefore, Up<sub>4</sub>A can play a functional role in the vascular system both under physiological and pathophysiological conditions.

This paper focuses on the effects of Up<sub>4</sub>A on vascular tone and its putative role on vascular function.

## 2. Up<sub>4</sub>A and Vascular Tone under Physiological Conditions

Several reports demonstrated that Up<sub>4</sub>A 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<sub>4</sub>A possesses both purine and pyrimidine moiety, these studies mainly focus on the relationship between Up<sub>4</sub>A 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 A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub> [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<sub>4</sub>A affects vascular tone and discuss the relevant mechanisms involved in Up<sub>4</sub>A responses.

**2.1. Aorta (Rat).** Linder et al. [31] characterized the effect of Up<sub>4</sub>A in thoracic aorta from rats using isometric tension recording. In intact aortic rings precontracted with phenylephrine, Up<sub>4</sub>A treatment led to a modest endothelium-dependent relaxation. On the other hand, under basal conditions, Up<sub>4</sub>A 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<sub>4</sub>A-induced contraction in thoracic aorta. Linder et al. [31] further found that Up<sub>4</sub>A-induced contraction was suppressed by P1 (8-PST [32]) or P2X (NF279 [33]) receptor antagonists, L-type Ca<sup>2+</sup> channel blockade (nifedipine [34]), and Rho-kinase inhibition (Y27632 [35]). These results suggested that Up<sub>4</sub>A-induced contraction is modulated by NO, mediated by P1 and P2X receptor activation, and involves L-type Ca<sup>2+</sup> channels and Rho-kinase activation in smooth muscle cells. Moreover, Up<sub>4</sub>A-induced contraction was attenuated by a membrane permeable superoxide scavenger (tempol) and by an NADPH oxidase inhibitor (apocynin) suggesting that superoxide generation affects Up<sub>4</sub>A-induced contractile responses [31].

**2.2. Pulmonary Artery (Rat).** Gui et al. [36] characterized the effect of Up<sub>4</sub>A in pulmonary artery from rats using isometric

TABLE 1: Up<sub>4</sub>A and vascular reactivity.

Artery/tissue	Animal	Response	Putative receptor	Signaling	Reference
Thoracic aorta	Rat	Contraction Relaxation	P1, P2X	L-type Ca <sup>2+</sup> channel Rho kinase Superoxide NO (endothelium-dependent)	[31]
Pulmonary artery	Rat	Contraction	P2Y	Ca <sup>2+</sup> (extracellular and intracellular stores)	[36]
Thoracic aorta	Mouse	Contraction Relaxation			[41]
Perfused kidney	Rat	Contraction Relaxation	P2X <sub>1</sub> , P2Y <sub>2</sub> , P2Y <sub>4</sub> P2Y <sub>1</sub> , P2Y <sub>2</sub>	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<sub>4</sub>A responses. Up<sub>4</sub>A induced concentration-dependent contraction of isolated rat pulmonary arteries. Up<sub>4</sub>A 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<sub>4</sub>A -induced contraction was blocked by suramin, but not by P2X receptor antagonist (Ips<sub>1</sub>I) or desensitization of P2X receptors with α,β-methylene-ATP [36]. Up<sub>4</sub>A -induced contraction was inhibited by pretreatment with an inhibitor of Ca<sup>2+</sup> release from sarcoplasmic reticulum (thapsigargin), a Ca<sup>2+</sup> channel blocker (niflumidine) and a Ca<sup>2+</sup> chelator (EGTA), but unaffected by a Rho-kinase inhibitor (H-1152) [36]. Moreover, unlike ATP and UTP, Up<sub>4</sub>A does not induce vasodilation of endothelium-intact preparations contracted with phenylephrine [36]. These results suggest that Up<sub>4</sub>A 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<sub>4</sub>A involves the entry of extracellular Ca<sup>2+</sup> and release of Ca<sup>2+</sup> from intracellular stores but not Ca<sup>2+</sup> sensitization due to the activation of RhoA/Rho kinase pathway in vascular smooth muscle cells. Therefore, Up<sub>4</sub>A 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<sub>4</sub>A stimulated vasoconstriction mainly via P2X<sub>1</sub> receptors and probably also via P2Y<sub>2</sub> and P2Y<sub>4</sub> receptors. Very recently, findings from this same group indicate that in the rat perfused kidney, in addition to smooth muscle P2X<sub>1</sub> receptor-mediated vasoconstriction, Up<sub>4</sub>A showed concentration-dependent P2Y<sub>2</sub> receptor-mediated, long-lasting vasoconstriction [37]. Moreover, they demonstrated that Up<sub>4</sub>A-induced vasoconstriction was followed by vasodilation mediated by P2Y<sub>1</sub> and P2Y<sub>2</sub> receptor activation on endothelial cells leading to the release of NO [37].

In mouse vessels, Up<sub>4</sub>A 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<sub>4</sub>A may be due to the lack of P2X<sub>1</sub> receptors, which are the main target of Up<sub>4</sub>A, in postglomerular arterioles [39]. Therefore, it may be assumed that Up<sub>4</sub>A contributes to the regulation of glomerular perfusion, intraglomerular pressure, and glomerular filtration rate. Moreover, Up<sub>4</sub>A 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<sub>4</sub>A from tubule cells approximately 10-fold [38]. The release of Up<sub>4</sub>A from renal tubular cells may affect renal perfusion. Up<sub>4</sub>A release may further contribute to renal vascular autoregulation mechanisms [19, 40].

These results suggest that Up<sub>4</sub>A 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<sub>4</sub>A in aorta from mice using isometric tension recording and *in vivo* arterial pressure measurements in conscious mice and rats (see below). Up<sub>4</sub>A has both relaxing and contracting effects depending on the Up<sub>4</sub>A concentration, the presence of precontraction, and the mode of stimulation (namely, single versus cumulative dose/concentrations). Up<sub>4</sub>A produced contraction in mouse aorta. In rings precontracted with phenylephrine, Up<sub>4</sub>A induced relaxation. A pronounced transient contraction was observed when 10<sup>-5</sup> M Up<sub>4</sub>A was added as a bolus, while vasodilation was predominant when Up<sub>4</sub>A was added cumulatively. The contraction induced by low concentrations of Up<sub>4</sub>A was abolished by a cyclooxygenase inhibitor (indomethacin), suggesting that Up<sub>4</sub>A-induced contraction may be attributable to cyclooxygenase metabolites. Therefore, Up<sub>4</sub>A can evoke both relaxation and contraction in mouse aorta as well as rat aorta [31].

*2.5. Up<sub>4</sub>A Affects Arterial Blood Pressure In Vivo (Rat and Mouse).* Jankowski et al. [14] investigated the effects of Up<sub>4</sub>A on mean arterial pressure of rats. Both noradrenaline and Up<sub>4</sub>A 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<sub>4</sub>A showed a more prolonged effect on arterial blood pressure.

Hansen et al. [41] determined the effects of Up<sub>4</sub>A on mean arterial pressure in conscious mice and rats. Intravenous infusion of increasing doses of Up<sub>4</sub>A 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<sub>4</sub>A (namely, single dose versus step-up doses). Future experiments need to be performed to address this question.

Table 1 and Figure 1 summarize Up<sub>4</sub>A effects on various arteries from different species.

### 3. Up<sub>4</sub>A and Pathophysiological States

There is evidence that Up<sub>4</sub>A might have implications in the pathogenesis of human arterial hypertension. Jankowski et al. [42] demonstrated that the plasma concentrations of Up<sub>4</sub>A are increased in juvenile hypertensive humans compared with normotensive subjects. Up<sub>4</sub>A concentration significantly correlates with the left ventricular mass and intima/media wall thickness in the hypertensive patients [42]. Therefore, Up<sub>4</sub>A may have an association with hypertension and hypertension-related vascular abnormalities.

As mentioned above, so far, the studies of Up<sub>4</sub>A-mediated responses have been carried out only in normal animals, and there is no study to indicate the vascular effects of Up<sub>4</sub>A under pathophysiological conditions, such as arterial hypertension. Since the vascular responsiveness to Up<sub>4</sub>A 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<sub>4</sub>A produced concentration-dependent contractions in segments of renal and pulmonary arteries at basal resting tension [43]. In DOCA-salt rats [versus its control uninjected (Uni) rats], Up<sub>4</sub>A-induced contraction was similar in pulmonary artery and greater in renal artery [43]. Up<sub>4</sub>A-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 (I<sub>p5</sub>I). Furthermore, selective P2Y<sub>2</sub> agonist-(2-Thio-UTP-), P2Y<sub>2</sub>/P2Y<sub>4</sub> agonist-(UTPyS-), and P2Y<sub>6</sub> agonist-(MRS2693-) induced contractions were all increased in renal artery from DOCA-salt rats. Renal arterial protein expression of P2Y<sub>2</sub>, P2Y<sub>4</sub>, and P2Y<sub>6</sub> 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<sub>4</sub>A-induced contraction was reduced by an ERK pathway inhibitor (PD98059), and ERK activation stimulated by Up<sub>4</sub>A 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<sub>4</sub>A-induced contraction in renal artery from DOCA-salt hypertensive rats. Moreover, we recently observed that, in DOCA-salt rats (versus Uni rats), Up<sub>4</sub>A-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<sub>4</sub>A-induced contraction is heterogeneously affected among several vascular beds in DOCA-salt hypertensive rats. These results indicate that abnormal Up<sub>4</sub>A-induced contraction may be associated with the vascular dysfunction seen in hypertension.

Jankowski et al. [42] also found that Up<sub>4</sub>A 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<sub>4</sub>A 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 atherosclerosis [54–57], Up<sub>4</sub>A may play a potential role in the development of atherosclerosis.

Schuchardt et al. [58] investigated the influence of Up<sub>4</sub>A 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<sub>4</sub>A induced MCP-1 expression and secretion in VSMCs through the activation of P2Y<sub>2</sub> receptor in a concentration-dependent manner. MCP-1 formation depended on generation of ROS. Up<sub>4</sub>A-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<sub>4</sub>A stimulated Rac1 activation and p47<sup>phox</sup> 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<sub>4</sub>A-mediated intracellular signal transduction [58]. These results clearly demonstrated that Up<sub>4</sub>A induces NOX1-dependent ROS production, which further stimulates MCP-1 formation through MAPK phosphorylation in VSMCs. This process requires the activation of P2Y<sub>2</sub> receptor. Thus, Up<sub>4</sub>A is not only a potent EDCF but also a potent inducer of proinflammatory response in the vascular wall.

Moreover, Up<sub>4</sub>A 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<sub>4</sub>A 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<sub>4</sub>A on vascular function in physiological and pathophysiological states. Although Up<sub>4</sub>A 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<sub>4</sub>A? To what extent are there regionally differences in Up<sub>4</sub>A kinetics? Are there mechanisms modified in vessels under physiological and pathophysiological states? How and to what extent do Up<sub>4</sub>A receptor(s) interact with Up<sub>4</sub>A putative degradation forms (e.g., mononucleotides and nucleotides) in the vascular system? How do the vascular actions of Up<sub>4</sub>A 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<sub>4</sub>A specific receptor) should also be investigated in physiological and pathophysiological states. A comprehension of the vascular effects of Up<sub>4</sub>A in other cardiovascular diseases, such as atherosclerosis, diabetes, and stroke should also be encouraged.

A better understanding of the role of Up<sub>4</sub>A on vascular function and the regulation of Up<sub>4</sub>A 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 conflicts of interests, financial or otherwise, are declared by the authors.

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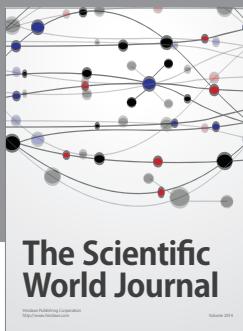
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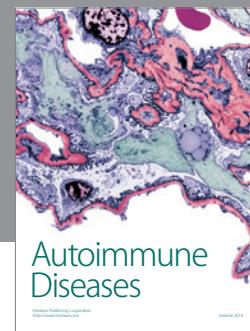
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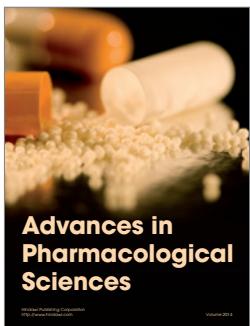
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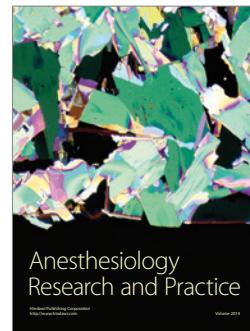


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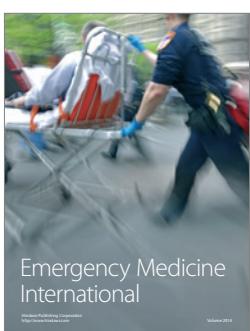
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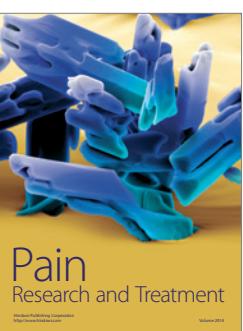
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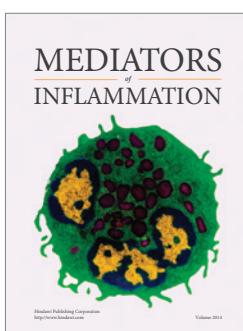
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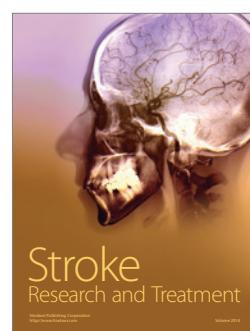
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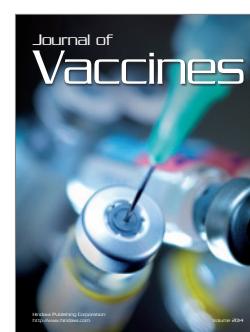
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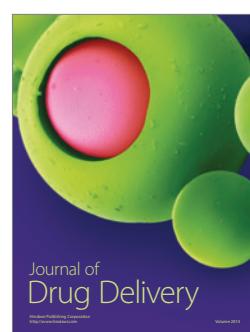
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