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Prostanoid Receptors in the Human Vascular Wall

Xavier Norel

INSERM U698: Haemostasis, Bioengineering and Cardiovascular Remodeling CHU X. Bichat, secteur C. Bernard, 46 rue Henri Huchard, 75877 Paris Cedex 18, France

E-mail: xnorel@hotmail.com

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The mechanisms involved in vascular homeostasis and disease are mostly dependent on the interactions between blood, vascular smooth muscle, and endothelial cells. There is an accumulation of evidence for the involvement of prostanoids, the arachidonic acid metabolites derived from the cyclooxygenase enzymatic pathway, in physiological and/or pathophysiological conditions. In humans, the prostanoids activate different receptors. The classical prostanoid receptors (DP, EP_{1-4}, FP, IP, and TP) are localized at the cell plasma or nuclear membrane. In addition, CRTH2 and the nuclear PPAR receptors are two other targets for prostanoids, namely, prostacyclin (PGI_2) or the natural derivatives of prostaglandin D_2. While there is little information on the role of CRTH2, there are many reports on PPAR activation and the consecutive expression of genes involved in the human vascular system. The role of the classical prostanoid receptors stimulated by PGI_2 and thromboxane in the control of the vascular tone has been largely documented, whereas the other receptor subtypes have been overlooked. There is now increasing evidence that suggests a role of PGE_2 and the EP receptor subtypes in the control of the human vascular tone and remodeling of the vascular wall. These receptors are also present on leukocytes and platelets, and they are implicated in most of the inflammatory processes within the vascular wall. Consequently, the EP receptor subtypes or isoforms would provide a novel and specific cardiovascular therapeutic approach in the near future.

KEYWORDS: prostaglandin, prostacyclin, thromboxane, endothelium, smooth muscle, vasoconstriction, vasodilatation, leukocyte, angiogenesis, migration, proliferation, atherosclerosis, hypertension, aneurysm, PGI_2, PGE_2, EP_1, EP_2, EP_3, EP_4, PPAR, CRTH2, COX-1, COX-2

Prostanoids (prostaglandin [PG] and thromboxane [Tx]) are derived from membrane phospholipids and the metabolism of arachidonic acid via the rate-limiting enzyme prostaglandin H synthase more commonly known as cyclooxygenase (COX). After the initial synthesis of PGH_2, the production of the other prostanoids will depend on the different respective prostanoid synthase, such as PGE-synthase (PGES) for PGE_2. The synthesis of prostanoids implicated in vascular homeostasis is dependent on the presence or absence of each enzymatic activity in the different cells of the blood or the vascular wall.

The different effects of prostanoids are also dependent on the activation of specific receptors, namely, the eight classical prostanoid receptors (DP, $EP_{1–4}$, FP, IP, and TP; Table 1), as well as the recently described chemoattractant receptor CRTH2 and nuclear receptors (PPARα,δ,γ). There is a considerable amount of information on the prostanoid receptors in mice and this will be treated in paper Matsuoka et al[162]. The present review will focus only on the human prostanoid receptors. In the nomenclature for the classical prostanoid receptors, the first letter indicates the prostanoid with the greatest affinity for this receptor. In addition, some isoforms derived from splice variants have been described in human tissues for the EP_3 receptor ($EP_{3\text{-I}}$, $EP_{3\text{-II}}$, $EP_{3\text{-III}}$, $EP_{3\text{-IV}}$, $EP_{3\text{-V}}$, $EP_{3\text{-VI}}$, $EP_{3\text{-e}}$, $EP_{3\text{-f}}$)[1], the FP receptor (FP-A, FP-B), and the TP receptor (TP-α, TP-β)[2]. These receptors, as well as the CRTH2, are found on the cytoplasmic membranes and they are seven transmembrane domain G-protein coupled receptors (Table 1). Their activation leads to increased or decreased production of different intracellular second messengers (Table 1). This situation has been further complicated by the increasing evidence for the presence of the classical prostanoid receptors at the nuclear and/or perinuclear region[3]. The prostanoid receptor localized on the plasma membrane elicits immediate physiological actions, whereas the nuclear one conveys gene regulation. Finally, in order to characterize these different prostanoid receptors, specific pharmacological tools (Table 1) and primers for molecular biology have been described[4,5,6].

TABLE 1
Types and Subtypes of Classical Prostanoid Receptors*

Prostanoid Receptor (Swiss-Prot n°)	Cloning Ref.	G-Protein Coupled	Second Messengers	Synthetic Agonist	Synthetic Antagonist
DP (Q13258)	[7]	Gs	cAMP ↑	BW245C; L644698	BWA848C; AH6809; ONO-AE3-237
EP_1 (P34995)	[8]	Unknown	Ca^{2+} ↑	17-Ph-PGE_2; Iloprost; Sulprostone	AH6809; SC-19220; SC-51322; ONO-8713
EP_2 (P43116)	[9]	Gs	cAMP ↑	Butaprost; AH13205; ONO-AE1-259; Misoprostol	AH6809
EP_3 (P43115)	[1]	Gi (Gs, Gq)	cAMP ↓ (cAMP ↑, IP3 ↑)	ONO-AE248; SC-46275; GR-63799; M&B-28767; Sulprostone; Misoprostol	L826266
EP_4 (P35408)	[10]	Gs	cAMP ↑	ONO-AE1-329; L-902688; Cicaprost	EP4A; AH23848; AH22921; GW627368X
FP (P43088)	[11]	Gq	IP3 ↑	Latanoprost; Fluprostenol; Cloprostenol	
IP (P43119)	[12]	Gs (Gq)	cAMP ↑ (IP3 ↑)	Cicaprost; Iloprost; Beraprost	RO1138452
TP (P21731)	[13]	Gq (Gi, Gs)	IP3 ↑ (cAMP ↓ ↑)	U46619; STA_2	BAY u3405; GR32191; AH23848

* Molecular and pharmacological characteristics of human prostanoid receptors derived from Swiss-Prot (http://www.expasy.org/sprot/) and IUPHAR (http://www.iuphar-db.org/iuphar-rd/index.html) web sites. The G-proteins and their respective second messengers are indicated in parenthesis when they are not the major one associated with this receptor[14,15].

PROSTANOID PRODUCTION IN THE HUMAN VASCULAR WALL

The cell or tissue production of prostanoids is dependent on physiological conditions. In normal physiological conditions, prostanoid synthesis is dependent on the COX-1 activity, the constitutive enzyme isoform. The synthesis and release occurs a few minutes after cell or tissue stimulation. In vascular preparations submitted to inflammatory conditions, hypoxia, shear stress, or mechanical perturbation (gravity, stretching) for several hours, the expression of COX-2 and other prostanoid synthase isoforms can be observed.

In normal physiological conditions, the release of PGI_2 quantified by the measurement of its stable metabolite (6-keto-$PGF_{1\alpha}$) has been largely described in human endothelial cells in culture after stimulation with thrombin, histamine, adenosine nucleotides (ADP, ATP), and bradykinin[16,17]. In fresh isolated vascular preparations, acetylcholine, serotonin, or leukotrienes induced endothelium-dependent relaxations[18,19,20,21]. These responses were partially inhibited by a nonselective COX inhibitor (indomethacin) and they are dependent on PGI_2 release by the endothelium. In these vascular cells or tissue, the production of PGI_2 was two- to eightfold greater in comparison with the other prostanoids synthesized[22,23]. These measurements are dependent on the initial COX-1 activity and not the COX-2 activity, since immunohistochemistry experiments and/or western-blot analysis have shown a preferential presence of the COX-1 in the endothelium of ovarian, pulmonary, or aortic vessels [24,25,26,27].

In the human endothelial cells in culture submitted to hypergravity during a period of 24–48 h, the induced expression of COX-2 was observed in association with an increased production of PGI_2[28]. Similar effects are observed with the human umbilical vein endothelial cells (HUVEC) under shear stress conditions[29]. Under hypoxia (2 h), the synthesis and the release of $PGF_{2\alpha}$ are induced in human coronary endothelial cells, human microvascular endothelial cells (HMEC), and HUVEC in culture[30]. In addition, cytokines (interleukin [IL]-1α/β; tumor necrosis factor [TNF]-α), angiotensin II (Ang II), arginine-vasopressine (AVP), certain growth factors (epidermal growth factor [EGF], transforming growth factor [TGF]-α), and endothelin-1 (ET-1) induce the synthesis and release of PGI_2 and PGE_2 in the majority of the human endothelial cells in culture[31,32,33,34]. These productions are detectable after a few hours of stimulation, implying the induction of the COX-2 isoform in the majority of the cases[31,35,36]. Furthermore, one of the PGES isoforms, the microsomal PGES-1 (mPGES-1), has received much attention because this enzyme is inducible and functionally linked with COX-2 expression. The presence of the transcript coding for the mPGES-1 and the protein after 3 h of HUVEC stimulation with IL-1β has been detected[37]. However contradictory results were described[38].

After a few hours of incubation of human vascular smooth muscle cells (HVSMC) with cytokines (IL-1β, TNF-α) and bacterial lipopolysaccharides (LPS), an increased production of PGI_2 and PGE_2 was also observed in the culture medium[38,39]. Other authors showed that these effects were associated with an induction of the COX-2 isoform[40,41]. For example, the muscular cells of human pulmonary artery in culture (HPASMC) under conditions of hypoxia or in the presence of cytokines express COX-2[25]. HPASMC incubated for 3 h with cytokines and successively stimulated with bradykinin or thrombin for a few minutes have a striking enhanced production of PGI_2[42,43]. In these previous studies, PGE_2 was not measured. The human fibroblasts are also present in the vascular wall. These cells, after 20 h of CD40 interaction with its ligand express COX-2 and the production of PGE_2 by these cells, are increased by a factor 10[44]. In the HVSMC and the human fibroblasts in culture, PGES transcript is present and its expression is increased in the presence of cytokines[38].

As an illustration of the previous experimental results on cell cultures, there is an increased presence of COX-2 and the inducible enzyme responsible for PGE_2 synthesis (mPGES-1) detected by immunocytochemistry in the carotid atherosclerotic plaque of symptomatic patients vs. the asymptomatic ones[45]. In conclusion, in most vascular cells, PGI_2 is the major biological active prostanoid produced under normal physiological conditions and when not the case, PGI_2 and PGE_2 are both equally produced as a consequence of the COX-2 induction.

CELLULAR LOCALISATION OF CLASSICAL PROSTANOID RECEPTORS

The location of the prostanoid receptors are mainly described in the vascular smooth muscle layer. That is supported by the immunohistochemistry data[46], by the physiological responses of isolated smooth muscle cells[47,48], and by the contraction/relaxation of isolated vascular preparations without endothelium[49,50]. For example, the vasoconstriction of human mammary or pulmonary arteries induced by the TP agonist U46619 was not modified in absence of endothelium[51,52]. On the other hand, there is also some evidence that suggests the presence of prostanoid receptors in human endothelium. The involvement of the different TP isoforms has been described in differential control of HUVEC or renal HMEC migration, however, these results are dependent on the number of passages during cell culture[53,54,55]. In addition, the isolated human pulmonary veins show a greater sensitivity during the contraction induced by U46619 when the endothelium was removed[52]. In a similar way, the relaxation of human hand veins produced after PGE_2 or $PGF_{2\alpha}$ stimulation was reduced in the absence of endothelium, whereas those elicited by PGI_2 or PGE_1 were not modified[56]. These results suggest the presence of endothelial prostanoid receptors and the involvement of an endothelial relaxing factor in these veins. On the contrary, in the human radial artery, an endothelial contractile factor was suggested since a reduced sensitivity to U46619 is measured in absence of endothelium[51]. These endothelial factors could either be released after stimulation of an endothelial prostanoid receptor or by the endothelium in a mechanical way in response to the contraction of the underlying smooth muscle induced by the prostanoids.

NUCLEAR AND CRTH2 RECEPTORS ACTIVATED BY PROSTANOIDS

There are two kinds of vascular nuclear prostanoid receptors: the peroxisome proliferator activated receptor (PPAR) and the classical prostanoid receptors. The location and the role of these classical prostanoid receptors at the nuclear membrane or perinuclear level are a new area of research. Some studies provide evidence for EP_1, EP_4, and/or $EP_{3\text{-}I}$ receptors at the perinuclear region in endothelial cells of porcine cerebral microvessel and in human embryonic kidney cells (HEK293)[3,57]. These results have shown that the activation of the nuclear $EP_{3\text{-}I}$ receptor could modulate iNOS and eNOS gene transcription[57,58]. In addition, they are consistent with the nuclear localization of COX[59], providing a local production of PGE_2, the preferential endogenous agonist for the EP receptors. The IP receptor may also be present at the nuclear level since PGI-synthase, the enzyme responsible for the conversion of PGH_2 into PGI_2, is also detected and colocalized at the perinuclear level with COX-1 in human endothelial cell line, ECV304[59].

PPARα, PPARβ (previously δ), and PPARγ are the second kind of nuclear receptor activated by prostanoids with numerous roles in vascular biology. The PPAR are activated by some natural derivatives of PGD_2 (Δ12-PGJ_2, 15d-PGJ_2), in addition, PPARα and PPARβ may use prostacyclin as endogenous ligands[60]. However, there are many other endogenous PPAR activators, most of them are of lipidic origin and the predominant ligand remains to be determined for each PPAR subtype. Experiments of RT-PCR and western-blot showed that the PPAR are present in the HVSMC and endothelial cells in culture[60,61,62]. They are responsible for many physiological events, for example, the activation of PPARα receptors expressed in human aortic smooth muscle cells promotes their proliferation[59]. PPARγ has been systematically explored particularly with the synthetic agonists of the thiazolidinediones (TZD) class[60]. The activation of PPARγ *in vitro* inhibits the expression of various genes implicated in the proliferation, migration, and inflammatory response of the vascular cells[63]. On the other hand, in histological sections of human blood vessels, the PPARγ receptor is present in the endothelial cells, but absent in the smooth muscle[64,65].

The implication of PPARγ in vascular disease has been largely studied in atherosclerosis. The activation of this nuclear receptor controls the transcription of many genes (Ang II and TxA_2 receptors, Tx-synthase, ET-1, proteases, COX-2, and cytokines) having a role in vascular inflammation specifically

at the level of the atherosclerotic lesions[60,66]. Immunohistochemistry studies using human coronary arteries obtained from recipients of heart transplants have shown that PPARγ is strongly expressed by the macrophages present in early and intermediate atherosclerotic lesions[66]. In these cells under inflammatory conditions, PGJ_2, Δ12-PGJ_2, 15d-PGJ_2, and TZD inhibit the expression of genes coding for proinflammatory cytokines (TNF-α, IL-1β, IL-6)[67] and for inducible enzymes (iNOS and COX-2)[60,68]. In the same way, the transcription of the matrix metalloproteinase-9 (MMP-9) gene as well as the migration of the HVSMC is inhibited after activation of the PPARγ receptor[61].

The activation of PPARγ plays an essentially antiatherosclerotic role, thus *in vivo,* the activation of PPARγ by the TZD significantly reduces the evolution of the atherosclerosis in humans[69,70,71]. Rosiglitazone protects the vascular wall by reducing proinflammatory responses and the occurrence of coronary events in type-2 diabetic patients within 6 months after percutaneous coronary intervention. Similarly, PPARα ligands like the fibrates decrease the risk of coronary heart diseases and the progression of premature atherosclerosis in patients with type-2 diabetes[60]. In addition, some dual PPARα/γ ligands have recently been developed and show a combined efficacy in the treatment of global risk in patients with the metabolic syndrome or type-2 diabetes[60].

CRTH2 is another prostanoid receptor activated by PGD_2 and its metabolites. This receptor has been recently described in human Th2 lymphocytes, Tc2 lymphocytes, eosinophil, and basophil[72]. On the other hand, neutrophils, platelets, Th1 lymphocytes, and B and T cells do not express the CRTH2 receptor on their surface[72,73,74]. CRTH2 receptor is activated selectively by DK-PGD_2[74], a natural metabolite of PGD_2[75], and also by the 11-dehydro-TXB_2, one of the principal metabolites of TXA_2[76]. In addition, 15d-PGJ_2, can bind to CRTH2 receptor with an equivalent affinity in comparison with PGD_2 and DK-PGD_2[74]. The eosinophil migration induced by the activation of CRTH2 receptor is blocked by the TP/CRTH2 antagonist BAY u3405 (ramatroban)[77]. Lastly, the activation of this receptor by PGD_2 decreases the intracellular production of cAMP, while an opposite effect is observed after activation of DP receptor, the preferential classical receptor for PGD_2[78,79].

The first studies carried out on humans concerning CRTH2 primarily implicated this receptor with the inflammatory allergic response[80]. One of the principal biological functions induced by the activation of this receptor is chemotaxis. Thus PGD_2 or DK-PGD_2 causes the migration of eosinophil, basophil, and the Th2 lymphocytes[72]. These events concern the pulmonary vessels during allergic or asthmatic responses, however, the role of CRTH2 in cardiovascular diseases has not been studied.

PROSTANOID RECEPTORS IN HUMAN BLOOD CELLS

Blood cells and constitutive cells of the vascular wall permanently interact during healthy and pathological conditions. Two of these classical cell-cell interactions are the endothelial synthesis of PGI_2 from PGH_2 released by platelets and the synthesis of TxA_2 by platelets from PGH_2 released by the endothelial cells. These events are associated with hemostasis including the activation of prostanoid receptors present both in platelets and in cells of the vascular wall. Similar communication between blood cells and the endothelium exists during the inflammatory processes, implicating blood cell extravasations in vascular diseases, such as atherosclerosis, aneurysm, or during allergy and edema. Leukocyte rolling, adhesion, and migration through the endothelial cells are dependent on prostanoid receptor activation. For example, PGE_2 or PGE_1 can block the leukocyte migration through human endothelial cells in culture[81,82]. The different prostanoid receptors described in human blood cells and involved in these different events are indicated in Table 2.

TABLE 2
Prostanoid Receptors in Human Blood Cells*

Cells	Receptors		Induced Effects (+ Activation, – Inhibition)	Ref.
Platelet	DP, IP	–	Aggregation	[83]
	TP, EP_3	+	Aggregation	[83]
Erythrocyte	TP	+	Membrane destabilization	[84]
	IP	+	Insulin binding, membrane stabilization	[84,85]
Eosinophil	EP_4	–	Production of LTC_4	[86]
	DP	–	Apoptosis; adhesion	[73,78]
Neutrophil	EP_2, DP	–	LTB_4 and superoxide anion release	[87]
	DP	–	Migration	[88]
	FP	+	Migration	[30]
Basophil	IP, DP	+	cAMP production	[89]
Mastocyte	EP_2	+	Vascular endothelial growth factor (VEGF) production	[90]
Monocyte	EP($_2$ or $_4$), IP	–	TNF-α production	[91]
	EP_2, EP_4	+	Maturation in monocyte derived dentritic cell	[92]
	EP_2, EP_4	–	Intercellular adhesion molecule-1 (ICAM-1; B7) expression	[93]
	EP($_2$ or $_4$)	+	COX-2 expression	[94]
	EP_4	–	IL-12 production	[95]
	EP_3	+	Migration	[96]
	IP	+	VEGF production	[97]
	TP	–	Migration, cell adhesion	[98]
Macrophage	EP_4	–	Chemokine production	[99]
	EP_4	+	IL-6 production	[4]
	EP($_2$ or $_4$)	+	Migration	[100]
B Lymphocyte	EP_4		EP_4 mRNA expression	[101]
T Lymphocyte	EP_3	+	Matrix metalloproteinase 9 (MMP-9) production	[102]
	EP_4	–	IL-2 production	[103]
	EP_4	+	IL-6 production	[104]
	EP_2	–	Apoptosis	[105]

* Prostanoid receptors described in human blood cells and the induced effects after their stimulation. (Receptors absent or not determined were not distinguished.)

ANGIOGENESIS AND THE PROSTANOID RECEPTORS

The proliferation of vascular smooth muscle cells (HVSMC) derived from the human pulmonary artery induced by fetal calf serum is inhibited by PGI_2, PGE_2, or cicaprost [41,48,106]. These results suggest activation of the IP receptor and probably that of an EP receptor during this effect. The activation of IP receptor by iloprost also reduces the migration induced by endothelial cell–conditioned medium as chemoattractant of the HVSMC derived from mammary artery[47]. A recent study based on microarray[107] confirmed the inhibitory role of IP receptors in the proliferation and the migration of the HVSMC. These authors showed that stimulation by iloprost modifies the expression of 83 genes in the HVSMC. Some of these genes (zinc finger transcription factor [hEZF], growth arrest specific gene 1

[gas1], VEGF, cysteine-rich angiogenic protein [Cyr61]) are known to be implicated in smooth muscle growth and cell migration[107,108].

The incubation of aorta HVSMC with PGE_2 decreased the cellular proliferation and the DNA synthesis[109]. These authors suggested the involvement of the EP_1 receptors since this inhibition was observed with PGE_2 while PGE_1 was ineffective. The pharmacological characterization of this receptor remains to be confirmed since another study showed that PGE_1 and PGE_2 inhibited the growth of these cells[110]. In addition, the agonists of the EP receptors can also control the migration of HVSMC. The migration of HVSMC derived from pulmonary artery induced by platelet-derived growth factor (PDGF) is inhibited by PGE_2[111]. PGE_2 elicited this effect with an efficacy associated with its ability to promote cAMP accumulation and PKA activation. This intracellular signaling suggests an inhibition of the migration mediated by an $EP_{2/4}$ receptor. On the contrary, M&B28767, the selective agonist for EP_3 receptors, stimulates the migration of the HVSMC derived from the mammary artery[47]. Finally, similar control of the endothelial cell chemotaxis by PGE_2 and thromboxane has been described; the HUVEC migration induced by IL-1β are partially blocked by EP_4, or TP-selective antagonists[112].

The COX-2 activity participates in angiogenesis observed in different models, such as rodent corneas[112,113], proliferation of human endothelial cell culture[114], or in pathophysiological conditions, such as diabetic and ischemic retinopathy[115]. Prostanoids derived from the COX-2 activity play a key role in oncogenesis since an increased expression of this enzyme has been detected in colon, breast, gastric, lung, and pancreatic cancers[116]. More specifically, the association of the COX-2 activity with angiogenesis in different forms of human cancer is well documented. An elevated COX-2 expression is detected with lymph node metastases and reduced survival in Barrett's cancer. This event appears to be related to the induction of angiogenesis and proliferation[117]. The COX-2 expression correlates with microvessel density and VEGF production in the angiogenesis of human non-small cell lung cancer[118]. Hepatocellular carcinoma is a highly malignant tumor characterized by active neovascularization; the VEGF production and venous invasion correlate with COX-2 activity[119]. The COX-2 inhibitors reduce tumor induced angiogenesis when xenografts of human colon cancer cells are planted in murine hosts[113]. However, the prostanoid receptors involved in human tumor angiogenesis are not known, while the EP_3 subtype has been suggested in mice models of angiogenesis and tumor growth[120].

PROSTANOID RECEPTORS INVOLVED IN THE HUMAN VASCULAR TONE

When the receptors are localized on the smooth muscle, the activation of IP, EP_2, EP_4, or DP receptors by prostanoids induces vasodilatation, while the activation of TP, EP_1, EP_3, or FP receptors is responsible for vasoconstrictions[121]. Most of the studies on vascular tone (Table 3) describe contractions produced by the TxA_2 analog (U46619) and relaxations induced by the PGI_2 analogs (iloprost or cicaprost). These results indicate that most human vascular smooth muscle expresses TP and IP receptors (Table 3). However, in these studies, the involvement of the IP receptor should be considered with caution since iloprost and, particularly, cicaprost have recently been described as potent agonists for the EP_4 receptor subtype[122,123,124].

There are very few studies concerning the involvement of other prostanoid receptor subtypes (EP, FP, or DP; Table 3) in the control of the vascular tone, although there is increasing evidence for the presence and a role for the four EP receptor subtypes preferentially stimulated by PGE_2[125,126,127,128,129,130]. In addition, a characterization of the EP receptors should be of interest since there is a striking increase in the quantities of the inducible mPGES-1 under inflammatory conditions and, in consequence, an increased concentration of PGE_2 in the vascular wall or in the blood of atherosclerosis patients[131,132].

TABLE 3
Prostanoid Receptors Involved in the Control (*In Vivo* or *In Vitro*) of Human Vascular Smooth Muscle Tone*

Vascular Preparations	Receptor Involved in		Ref.
	Vasoconstriction	Vasodilatation	
Basilar artery	TP, $EP_?$	IP	[133]
Cerebral artery	TP	IP, EP_4	[127]
Pial artery	TP	IP	[134,135]
Retinal arteriole	TP	DP	[136]
Coronary artery	TP	IP	[137,138,139]
Mammary artery	TP		[51]
Thymic artery	TP		[140]
Pulmonary artery	TP, EP_3	IP	[128,130,141,142,143]
Pulmonary vein	TP, EP_1	IP, DP, $EP_?$	[129,130]
Gastroepiploic artery	TP		[49,51]
Gastroepiploic vein	TP		[49]
Mesenteric artery		IP	[138]
Brachial artery		IP	[144]
Radial artery	TP		[51]
Hand artery		IP	[145]
Hand vein	TP	IP	[145,146]
Uterine artery	TP	IP, EP_4	[126]
Placental artery	TP		[147]
Placental vein	TP		[148]
Umbilical artery	TP	IP	[147,149]
Umbilical vein	TP, FP		[147,148,150]
Penile artery	TP	IP, $EP_?$	[125]
Femoral artery	TP		[151]
Saphenous vein	TP		[152]

* In this table, only the prostanoid receptor subtypes described in the literature are indicated. $EP_?$ Indicates that a specific EP response to PGE_2 was observed, however, the EP subtype has not been characterized.

VASCULAR PATHOLOGIES AND THE CLASSICAL PROSTANOID RECEPTORS

The IP agonists — the synthetic PGI_2 (epoprostenol), PGE_1 (alprostadil), or the PGI_2 analogue iloprost — have been used for the last 20 years in the treatment of human pulmonary hypertension. These compounds decrease the pulmonary vascular resistance and may be administered by inhalation (iloprost) or continuous subcutaneous infusion, as in the case of treprostinil, the last PGI_2 analogue synthesized[153]. Intravenous injection of PGE_1 is also useful to maintain the patency of the ductus arteriosus in infants with certain cardiac malformations[5]. Similar to the treatment of these pathologies, in the near future, the prostanoid receptors will probably be new therapeutic targets for the treatment of other cardiovascular diseases. Changes in the density or appearance of new prostanoid receptor subtypes and isoforms in the vascular wall are associated with the development of cardiovascular pathologies.

This variation of receptorial expression is observed during atherosclerosis, for example, where the density of TP receptor is increased in the atherosclerotic coronary artery[46]. The EP_4 receptor is detected by immunohistochemistry in human carotid atherosclerotic plaques, in macrophage-rich lesions, and in smooth muscle, while no staining was observed in the vascular wall of normal carotid artery[99]. The EP_2 receptor has also been detected in these *atheroma* plaques[154]. In addition, in this study on HVSMC derived from the media of human internal mammary arteries, the activation of EP_2 and IP receptors induced an up-regulation of hyaluronic acid. This compound is a prominent constituent of the extracellular matrix in atherosclerotic vascular lesions in humans and is known to modulate the vascular smooth muscle phenotype. However, the transcription and expression of the EP_4 receptor in the human carotid atherosclerotic plaques are largely predominant in comparison to the EP_2 subtype[155]. In addition, a stronger expression and a greater detection was observed for the EP_4 receptor in the carotid atherosclerotic plaque of symptomatic patients vs. the asymptomatic ones[155]. The EP_4 receptor localized mainly in the macrophage-rich lesions, together with COX-2, mPGES-1, MMP-9, and MMP-2 [45,99,155]. The activation of this receptor by PGE_2 and the subsequent production of MMP probably contribute to the plaque destabilization.

In the previous studies, the appearance of the prostanoid receptors in the atherosclerotic vascular wall may be due to the migration of macrophages expressing these receptors and/or an induction of their expression by the constitutive cells of the vascular wall. As in the case of the inducible enzymes (COX-2, mPGES-1), it is not excluded that the proinflammatory conditions found in atherosclerosis may also stimulate the transcription of prostanoid receptors in the vascular cells. This induction has been observed with the increased expression of EP_2 and EP_4 receptors in human nonvascular cells, as occurs in the experiments with the synovial and cervical fibroblasts treated with IL-1β[156,157].

PGE_2 receptors in abdominal aortic aneurysm have been explored[4]. This study shows that the release of IL-6 by the aortic aneurysm wall is more specifically due to the activation of the EP_4 receptor present in the macrophages instead of the smooth muscle cells. The production of this proinflammatory cytokine mediates aneurysmal degeneration. The level of IL-6 measured postsurgery in the blood of patients with ruptured abdominal aortic aneurysms was significantly increased in nonsurvivors vs. survivors[158].

Another PGE_2 receptor, namely, the EP_3 receptor subtype, is implicated in the development of vascular pathologies. The DeCODE Company has developed an EP_3 antagonist (NG041) presently in phase IIa clinical trial. This compound is an example of the new drugs targeting the prostanoid receptors. Through their population genetic research in Iceland, this company has identified common versions of the gene encoding the EP_3 receptor that confer increasing risk of atherosclerosis[159]. These epidemiological data are in accordance with the different proatherogenic roles of the EP_3 receptor in human tissues, that is, vasoconstriction[128,160], migration of vascular smooth muscle cells[47], and platelet activation[83].

In a general way, the prostanoid receptor ligands used in cardiovascular therapeutics should at least stimulate the vasodilatation, block the vasoconstriction and inhibit the platelet aggregation. More specifically they should activate the IP- and DP- receptors and block the TP- and EP_3- receptors since these receptors are also present on human platelet[83]. In addition, from the data previously described in atherosclerotic and aneurismal tissues, development of specific antagonists for the receptors involved in the inflammatory processes of the vascular wall, such as EP_4, should be also useful.

CONCLUSION

After the cardiovascular risks encountered with the COX-2 inhibitors, new and more selective strategies have been developed to modulate the physiological effects mediated by prostanoids. The different prostanoid receptors, as well as the different enzymes of the cyclooxygenase pathway, such as the prostanoid synthases, will be future therapeutic targets for the treatment of cardiovascular pathologies. The PPARs have already become therapeutic targets through the use of the fibrate class and the insulin-sensitizing thiazolidinediones. These compounds are used to reduce the cardiovascular risk in patients

with atherosclerosis, metabolic syndrome, and/or diabetes. Furthermore, the different physiological roles of the classical prostanoid receptor subtypes and isoforms, the nuclear receptors, and the CRTH2 in the human vascular wall are intensively explored. In addition to PGI_2 and thromboxane, there is increasing evidence that suggests a key cardiovascular role for PGE_2. The four EP receptor subtypes activated by PGE_2 are present on the cells of the vascular wall, as well as in the blood cell during vascular inflammation. Their activation and, more specifically, the EP_3 and EP_4 receptor activation appears associated in most human physiological or pathophysiological responses of the vascular wall. For these reasons, these classical prostanoid receptors are also promising cardiovascular therapeutic targets.

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