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VIII. International Union of Pharmacology Classification of Prostanoid Receptors: Properties, Distribution, and Structure of the Receptors and Their Subtypes

ROBERT A. COLEMAN,[1] WILLIAM L. SMITH,[2] AND SHUH NARUMIYA[3]

[1]*Glaxo Research and Development, Ltd., Ware, Hertfordshire, England;* [2]*Department of Biochemistry, Michigan State University, East Lansing, Michigan, USA; and* [3]*Department of Pharmacology, Kyoto University Faculty of Medicine, Kyoto 606, Japan*

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I. Introduction

A. Historical Background

The activity associated with the PGs* was first observed in 1930 by Kurzrok and Lieb in human seminal fluid. This observation was supported and extended by both Goldblatt (1933) and von Euler (1934). However, it was not for another 20 years that Bergström and Sjövall (1957) successfully purified the first PGs, PGE_1 and $PGF_{1\alpha}$. During the next decade or so, it became clear that the biological activities of the PGs were extremely diverse and that the family included members other than the original two, these being named alphabetically from PGA_2 to PGH_2. Of these, PGA_2, PGB_2, and PGC_2 are prone to extraction artifacts (Schneider et al., 1966; Horton, 1979). PGG_2 and PGH_2 are unstable intermediates in the biosynthesis of this family of hormones (Hamberg and Samuelsson, 1973). PGs can be biosynthesized from three related fatty acid precursors, 8,11,14-eicosatrienoic acid (dihomo-γ-linolenic acid), 5,8,11,14-eicosatetraenoic acid (arachidonic acid), and 5,8,11,14,17-eicosapentaenoic acid (timodonic acid), giving rise to 1-, 2- and 3-series PGs, respectively (van Dorp et al., 1964); the numerals refer to the number of carbon-carbon double bonds present. In most animals, arachidonic acid is the most important precursor; therefore, the 2-series PGs are by far the most abundant.

By the middle 1970s it was clear that PGs were capable of causing a diverse range of actions, but few efforts were made to investigate the receptors at which PGs acted. Indeed, some doubted that they acted at receptors in the "classical" sense at all, believing, rather, that by virtue of their lipid nature they dissolved in cell membranes and caused their biological actions by altering the physical state of those membranes. However, despite this, interest was increasing in this new class of hormones, and there was optimism about their potential as new drugs. This interest peaked with the discovery of the two unstable PG-like compounds, TXA_2 (Hamberg et al., 1975) and PGI_2 (Moncada et al., 1976). The collective term for this family of hormones is "the prostanoids." At that time, the main problem with prostanoids as drugs was perceived to be one of stability, both chemical and metabolic, and there was an enormous amount of chemical effort directed toward developing more stable prostanoids. Despite successes in this regard, another problem soon became apparent, and that was one of side effect liability. Indeed, the very range of the actions of this class of compounds, which on the one hand offered such opportunities for drug development, began conversely to appear to be their limitation, because it appeared not to be possible to produce prostanoids as drugs without use-limiting side effects. It was this challenge that prompted a small number of groups of scientists to attempt to rationalise the "bewildering array" of actions of prostanoids by means of the identification and classification of prostanoid receptors. Initially, in the 1970s, most of the work directed toward the study of prostanoid receptors was designed to characterise specific binding sites for the radiolabeled natural ligands (Kuehl and Humes, 1972; Rao, 1973; Powell et al., 1974). Although this served to support the existence of specific membrane-binding sites, these sites may or may not have represented functional receptors.

B. Studies of Receptor Identification and Classification

1. Functional studies. The use of functional data to classify hormone receptors was pioneered by Ahlquist in 1948, in an attempt to classify the receptors responsible for the biological actions of the catecholamines, adrenaline and noradrenaline. Despite the limited tools at his disposal, the outcome of these studies was the classification of adrenoceptors into α and β subtypes, a classification scheme that has stood to the present day. This work was subsequently extended by Lands and colleagues

* Abbreviations: PG, prostaglandin; TX, thromboxane; PGI_2, prostacyclin; G_s, stimulatory G-protein; G_i, inhibitory G-protein; G_q, pertussis toxin-insensitive G-protein; RCCT, rabbit cortical collecting tubule.

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in 1967 who, using the same approach, demonstrated that, although the classification proposed by Ahlquist was essentially correct, it was an oversimplification and one of Ahlquist's receptors, the β-adrenoceptor, could be further divided into two subtypes, termed β_1 and β_2. This approach to receptor classification, although now largely taken for granted, was revolutionary.

The relatively large number of naturally occurring prostanoids, their high potencies, and the variety of the responses elicited by them in different cells throughout the mammalian body made this an ideal area in which to study receptor subtypes. This was first recognised by Pickles in 1967, when he demonstrated that a range of different prostanoids, both natural and synthetic, showed different patterns of activity on a variety of isolated smooth muscle preparations. Yet, Pickles did not extend this work, and during the next 15 years little further work was reported extending his original observations. The few studies that were published (Andersen and Ramwell, 1974; Andersen et al., 1980; Gardiner and Collier, 1980) demonstrated that not only were different rank orders of agonist activity observed with a relatively small range of both natural and synthetic prostanoids, over a wide range of isolated preparations, but certain consistent patterns emerged. However, this work was not developed to describe a comprehensive receptor classification. In 1982, Kennedy and his coworkers described a comprehensive, working classification of prostanoid receptors based on functional data with the natural agonists, some synthetic agonists, and a small number of antagonists (Kennedy et al., 1982; Coleman et al., 1984). Their classification of receptors into DP, EP, FP, IP, and TP recognised the fact that receptors exist that are specific for each of the five naturally occurring prostanoids, PGs D_2, E_2, $F_{2\alpha}$, I_2, and TXA_2, respectively. It was clear that at each of these receptors one of the natural prostanoids was at least one order of magnitude more potent than any of the other four. Although in hindsight this observation may not seem remarkable, there are to this day no other examples of a family of hormones that demonstate such receptor selectivity; it is certainly not true of catecholamines, tachykinins, or leukotrienes. Although this broad classification into five classes of prostanoid receptors remains intact, evidence arose for a subdivision within the EP receptor family. There is now evidence for the existence of four subtypes of EP receptors, termed arbitrarily EP_1, EP_2, EP_3, and EP_4. The recent cloning and expression of receptors for the prostanoids has not only confirmed the existence of at least four of the five classes of prostanoid receptor, EP, FP, IP, and TP, but has also supported the subdivision of EP receptors into at least three subtypes, corresponding to EP_1, EP_2 (or EP_4), and EP_3. The current classification and nomenclature of prostanoid receptors is summarised in table 1.

2. Radioligand-binding studies. During the 1970s, there were a large number of ligand-binding studies performed in a wide range of tissues using radiolabeled PGs (Robertson, 1986). These studies made it clear that there are specific prostanoid-binding sites in the plasma membranes of such diverse tissues as liver, smooth muscle, fat cells, corpus luteum, leukocytes, platelets, and brain. In many of these, the ligand affinity (K_d) is of the order of 1 to 10 nM, and the receptor density is in the range of 1 pmol/mg protein. Furthermore, in many of the tissues exhibiting high affinity, and high density prostanoid-binding sites, it was known that prostanoids had biological activity, thus providing circumstantial support for these binding sites being functional receptors. Nonetheless, these studies did not further our understanding of prostanoid receptor classification, because in most cases, radioligands were confined to [^{3}H]PGs E_1, E_2, or $F_{2\alpha}$, and either no competition studies were performed or competition studies were undertaken with prostanoids that do not discriminate among receptor subtypes (Coleman et al., 1990). It was not until the 1980s that studies were performed using [^{3}H]PGs D_2 and I_2, and the evidence for a wider range of different types of prostanoid ligand-binding site emerged.

That some of these binding sites truly represented functional receptors was supported by the demonstration that they were capable of autoregulation, whereby binding site numbers are modulated by exposure to ligand. Thus, exposure of the animal or tissue to high levels of unlabeled ligand resulted in a "down-regulation" or loss of binding sites (Robertson et al., 1980; Robertson and Little, 1983), and conversely, treatment with inhibitors of endogenous prostanoid synthesis led to a corresponding "up-regulation" of binding sites (Rice et al., 1981). In some of these studies, attempts were made to associate modulation of binding sites with alterations in function; for example, Richelsen and Beck-Nielsen (1984) demonstrated that down-regulation of PGE_2-binding sites was accompanied by a reduction in PGE_2-induced inhibition of lipolysis. However, it was not until more selective, synthetic prostanoid agonists and antagonists became available, and distinct rank orders of agonist activity in functional studies became apparent, that the association between binding sites and functional receptors became possible (see section I.B.3).

3. Second-messenger studies. Almost all of the studies of prostanoids and second messengers until the late 1980s were concerned with cyclic nucleotides, particularly cAMP. Butcher and colleagues were the first to demonstrate an association between PGs and cAMP (Butcher et al., 1967; Butcher and Baird, 1968), and although their observation made little initial impact, it became increasingly accepted that E-series PGs at least were capable of stimulating adenylyl cyclase to cause increases in intracellular cAMP (Kuehl et al., 1972, 1973). However, it became clear that prostanoid effects on adenylyl cyclase were not solely excitatory, and in 1972, a more complex

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TABLE 1

*Classification and nomenclature of prostanoid receptors, with selective agonists and antagonists, and system of response transduction**

Receptor/subtype	Selective agonists	Selective antagonists	Transduction system
DP	BW 245C, ZK110841, RS 93520	BW A868C, AH6809†	↑cAMP via G_s
EP			
EP_1	Iloprost,‡ 17-phenyl PGE_2, sulprostone‖	AH6809,[7]§ SC-19220	↑Intracellular Ca^{2+}
EP_2	Butaprost, AH13205, misoprostol‖	None	↑cAMP via G_s
EP_3	Enprostil, GR63799, sulprostone,¶ misoprostol,** M&B 28767††	None	↓cAMP via G_i ↑PI turnover via G_q
EP_4	None	AH22921,‡‡ AH23848‡‡	↑cAMP via G_s?
FP	Fluprostenol, cloprostenol, prostalene	None	↑PI turnover via G_q
IP	Cicaprost, iloprost, octimibate	None	↑cAMP via G_s
TP	U44069, U46619, SQ 26655, EP 011, I-BOP	AH23848,§§ GR32191, EP 092, SQ 29548, ICI 192605, L-655240, BAY u 3405, S-145, BM 13505	↑PI turnover via G_q

* For more detailed information, see relevant section in text.
† Also EP_1 receptor-blocking drug.
‡ Also IP receptor agonist.
§ Also DP receptor-blocking drug.
‖ Also EP_3 receptor agonist.
¶ Also EP_1 receptor agonist.
** Also EP_2 receptor agonist.
†† Also TP receptor agonist.
‡‡ Also TP receptor-blocking drug.
§§ Also EP_4 receptor-blocking drug.

relationship between PGEs and adenylyl cyclase was reported in platelets (Shio and Ramwell, 1972). PGE_1 caused an elevation of platelet cAMP, but PGE_2 caused a reduction. Interestingly, this distinction was reflected in the effects of PGE_1 and PGE_2 on platelet aggregation. PGE_1 inhibited aggregation, whereas PGE_2 potentiated the effect of aggregatory agents such as adenosine diphosphate (Shio and Ramwell, 1971). This parallel between cAMP and function not only provided evidence that the effect on cyclic nucleotide levels had functional relevance but also suggested that these might be receptor subtypes. A further distinction was observed at this time between the effects of E- and F-series PGs. Whereas PGE_1 and PGE_2 were seen to exert marked effects on levels of cAMP, both stimulatory and inhibitory, $PGF_{2\alpha}$, despite its marked functional activity in many different cell types, was virtually devoid of effect on cAMP (Kuehl and Humes, 1972; Smith et al., 1992). In fact, it became accepted that the actions of $PGF_{2\alpha}$ were mediated through elevation of cyclic guanosine 3′,5′-monophosphate (Dunham et al., 1974; Kadowitz et al., 1975), although this idea has now lost support.

As with studies of radioligand binding, studies of second-messenger systems in the 1970s were limited, there being few studies in which ranges of receptor-selective agonists were compared for both function and modulation of cyclic nucleotide levels. Where comparisons were reported, as with the binding studies, they involved comparisons of the then available PGs, E, F, A, and B (Kuehl and Humes, 1972), and these give little insight into the receptor subtypes involved (Coleman et al., 1990). It was not until the 1980s, when more selective agonists became available, that studies of intracellular levels of cAMP provided real evidence for the existence of prostanoid receptor subtypes (see section I.B.4).

4. Molecular biology. Development of highly potent TP receptor antagonists and introduction of their high-affinity radiolabeled derivatives in binding experiments in the 1980s enabled solubilization and purification of the TP receptor. Using one of these compounds, S-145 (table 2), and its ^3H-labeled derivative, Ushikubi et al. (1989) purified the human TP receptor from human platelets to apparent homogeneity, and based on the partial amino acid sequence of the purified protein, its cDNA was isolated in 1991 (Hirata et al., 1991). Subsequently, the cDNAs for numerous types and subtypes of prostanoid receptors have been cloned by homology screening, and the structures of the receptors that they encode have been elucidated. These receptors include the mouse TP receptor, the human EP_1 receptor, the mouse EP_1, EP_2,

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TABLE 2

Glossary of the chemical names of prostanoid agonists and antagonists quoted as code numbers in this review

Code	Chemical name
AH6809	6-isopropoxy-9-oxoxanthene-2-caboxylic acid
AH13205	*trans*-2-[4-(1-hydroxyhexyl)phenyl]-5-oxocyclo pentaneheptanoic acid
AH19437	1α(Z),2β,5α(±)-methyl,7-2-(4-morpholinyl)-3-oxo-5(phenylmethoxy)cyclopentyl-5-heptenoate
AH22921	[1α(Z),2β,5α]-(±)-7-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-5-heptenoic acid
AH23848	[1α(Z),2β,5α]-(±)-7-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid
AY23626	11-deoxy-prostaglandin E_0
BAY u 3405	3(*R*)-3-(4-fluorophenylsulphonamido)-1,2,3,4-tetrahydro-9-carbazole propanoic acid
BW 245C	5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl) hydantoin
BW A868C	3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino)-hydantoin
EP 011	17,18,19,20-tetranor-16-*p*-fluorophenoxy-9,11-etheno PGH_2
EP 045	(±)-5-*endo*-(6′-carboxyhex-2′Z-enyl)-6-*exo*[N-(phenylcarbamoyl)hydrazono-methyl]-*bicyclo*[2.2.1] heptane
EP 092	9α,11α-ethano-ω-heptanor-13-methyl-13-phenyl-thio-carbamoyl-hydrazino-prosta-5Z-enoic acid
EP171	10a-homo-15S-hydroxy-9α,11α-epoxy-16*p*-fluorophenoxy-ω-tetranor-5Z,13E-dienoic acid
FCE 22176	(+)-13,14-didehydro-20-methyl-carboprostacyclin
GR32191	[1*R*-[1α(Z)2β,3α,5α]]-(+)-7-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid
GR63799	[1*R*-[1α(Z),2β(*R**),3α]-(−)-4-benzoylamino)phenyl-7-[3-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl]-4-heptenoate
I-BOP	[1*S*-(1α2β(5Z),3α(1E,3*S**),4-α)]-7-[3-(3-hydroxy-4-(4′-iodophenoxy)-1-butenyl)-7-oxabicyclo-[2.2.1]heptan-2-yl]-5-heptenoic acid
ICI 192605	4(Z)-6-(2-*o*-chlorophenyl-1,3-dioxan-*cis*-5-yl) hexenoic acid
K 10136	13,14-didehydro-20-methyl $PGF_{2\alpha}$
L-655240	3-[1-(4-chlorobenzyl)-5-fluoro-3-methyl-indol-2-yl]2,2-dimethyl-propanoic acid)
M&B 28767	15S-hydroxy-9-oxo-16-phenoxy-ω-tetranorprost-13E-enoic acid
N-0164	Sodium *p*-benzyl-4-[1-oxo-2-(4-chlorobenzyl)-3-phenylpropyl] phenyl phosphonate
ONO-3708	(9,11)-(11,12)-dideoxa-9α,11α-dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14-oxo-15-cyclopentyl-16,17,18,19,20-pentanor-15-epi-TXA_2
RS 93520	Z-4-{(C3′*S*,1*R*,2*R*,3*S*,6*R*)-2C3′-cyclohexyl-3′-hydroxyprop-1-ynyl)-3-hydroxybicyclo[4.2.0]oct-7-ylidene} butyric acid
S-145	(1*S*,2*R*,3*R*,4*R*)-(5Z)-7-(3-[phenyl,sulphonyl-amino-bicyclo[2.2.1] hept-2-yl)hept-5-enoic acid
SC-19220	1-acetyl-2-(8-chloro-10,11-dihydodibenz[b,f][1,4]oxazepine-10-carbonyl) hydrazine
SQ 26655	(1*S*-(1a,2b(5Z),3a(1E,3*s**),4a))-7-(3-(3-hydroxy-1-octenyl)-7-oxabicyclo(2.2.1)hept-2-yl)-5-heptenoic acid
SQ 29548	[15-[1α,2β(5Z),3β,4α]-7-[3-[2-(phenylamino)-carbonyl]hydrazino] methyl]-7-oxobicyclo-[2,2,1]-hept-2-yl]-5-heptenoic acid
STA_2	9α,11α-thia-11a-carba-prosta-5Z,13E-dienoic acid
U44069	9α,11α-epoxymethano-15S-hydroxy-prosta-5Z,13E-dienoic acid
U46619	11α,9α-epoxymethano-15S-hydroxy-prosta-5Z,13E-dienoic acid
ZK110841	9-deoxy-9β-chloro-16,17,18,19,20-pentanor-15-cyclohexyl-$PGF_{2\alpha}$

and EP_3 receptors, the rat EP_3 receptor, the mouse and bovine FP receptors, and the mouse IP receptor. The deduced amino acid sequences of the recombinant mouse receptors are shown in figure 1. Hydrophobicity and homology analysis of these sequences has revealed that all of them have seven hydrophobic segments characteristic of transmembrane domains, indicating that they are G-protein-coupled, rhodopsin-type receptors. The overall homology among the receptors is not high, and the amino acid identity is scattered over the entire sequences, showing that they are derived from different genes. Indeed, Taketo et al. (1994) have identified the genetic loci of mouse EP_2, EP_3, and TP receptors on chromosomes 15, 3, and 10, respectively. On the other hand, as shown

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FIG. 1. Amino acid sequence alignment of the mouse prostanoid receptors. The amino acid sequences of the mouse PGF receptor (FP), TXA_2 receptor (TP), EP_1 receptor (EP_1), EP_3 receptor (EP_3), EP_2 receptor (EP_2), and PGI_2 receptor (IP) are aligned to obtain the optimum homology. The approximate positions of the putative transmembrane regions are indicated by horizontal lines above the sequences. Amino acids conserved are shown by bold letters.

in the figure, these receptors show strong conservation of sequence in several regions, indicating that they probably evolved from a common ancestor. The most conserved region is the seventh transmembrane domain, where the consensus sequence of L-X-A/Y-X-R-X-A-S/T-X-N-Q(P)-I-L-D-P-W-V(I)-Y(F)-I(L)-L-L/F-R is shared. Another region of significant homology is the second extracellular loop between the fourth and fifth transmembrane regions. Because these sequences are shared by the prostanoid receptors from various species, but not by other rhodopsin-type receptors, Narumiya et al. (1993) suggested that they are related to structural requirements of prostanoid recognition. Particular attention has been paid to the conserved arginine in the seventh transmembrane domain, which is located at a position analogous to lysine[296] of the bovine rhodopsin molecule that makes a Shiff base with its ligand, all-*trans*-retinal. In the rhodopsin-type receptor, ligand binding and recognition are suggested to occur in the outer half of the seven transmembrane segments (Savarese and Fraser, 1992). Because the carboxyl group is essential for biological activity of most prostanoids, it was proposed that the arginine serves as the binding site for the α-carboxyl group of prostanoid molecules. The other transmembrane domains of the prostanoid receptors are more hydrophobic than those of the monoamine receptors, which may facilitate binding to the cyclopentane ring and aliphatic side chains of prostanoid molecules.

All of the recombinant receptors have been expressed in cultured cells and their ligand-binding properties and signal transduction pathways studied. The results obtained with each receptor type are described in detail in subsequent sections. These studies may give us more accurate information than those obtained by pharmacological and biochemical studies in native tissues, because the expressed receptor system permits the study of homogeneous populations of receptors without the complication of the presence of other receptor types. Of course, there are also limitations to this approach. The fact that

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only the receptor cDNAs of a limited number of species have been cloned means that we do not know whether discrepancies between the properties of the recombinant receptors and the pharmacological analyses are attributable to species differences or to receptor subtypes (see discussion by Hall et al., 1993). Another limitation is that the recombinant receptors have been expressed and analysed only in Chinese hamster ovary cells or simian kidney COS cells, and this results in coupling of a receptor from one species with a G-protein from a different species; moreover, the pool of G proteins in CHO cells and COS cells may differ from that of the tissue in which a receptor is normally expressed. With prostanoid receptors, effects on the ligand-binding properties may be minimal, because, unlike the monoamine receptors, guanosine triphosphate analogues appear to exert little effect on prostanoid binding. Nonetheless, the ligand-binding profiles of the recombinant receptors (detailed in section II.A.2) are generally in good agreement with those characterized earlier in pharmacological and biochemical experiments.

II. Types, Subtypes, and Isoforms of Prostanoid Receptors

A. DP Receptors

1. Functional studies. a. SELECTIVE AGONISTS AND ANTAGONISTS. Although PGD_2 and various close analogues do behave as DP agonists, none is particularly selective (Giles and Leff, 1988). Indeed, PGD_2 itself possesses relatively potent FP and even TP receptor agonist activity. However, there are a number of potent and highly selective DP receptor agonists. One of these is 9-deoxy-Δ^9-PGD_2 (PGJ_2, Bundy et al., 1983), but the first to be identified, and the most widely used was BW 245C, a hydantoin prostanoid analogue (Caldwell et al., 1979). This compound is interesting in that it is at least one order of magnitude more potent than the natural ligand, PGD_2, as a DP receptor agonist but, on the other hand, appears to be several orders of magnitude less potent at other prostanoid receptors and lacks the relatively high FP and TP receptor agonist activity associated with PGD_2 itself. Since the discovery of BW 245C, another selective DP receptor agonist, ZK110841, was reported by Thierauch et al. (1988), although there is much less information concerning this compound. ZK110841 is interesting in that it is not an analogue of PGD_2 but of PGE_2. One additional compound of structural significance is RS 93520, which is superficially a PGI_2 analogue, and has some weak IP agonist activity but is much more potent as a DP receptor agonist (Alvarez et al., 1991). Quantitative data for some selective DP receptor agonists and antagonists are summarised in table 3.

The study of DP receptors has been facilitated by the availability of antagonists. The first compound shown to possess DP receptor-blocking activity was the phloretin derivative, N-0164, which weakly, but selectively, antagonised inhibitory activity of PGD_2 on human platelets (MacIntyre and Gordon, 1977). Subsequently, an EP_1 receptor-blocking drug, AH6809, was shown to exhibit DP receptor-blocking activity but was, again, rather weak, with a pA_2 of about 6.0 (Keery and Lumley, 1988). The most significant development was that of BW A868C (Giles et al., 1989), an analogue of the agonist, BW 245C. In fact, the Wellcome group synthesised a wide range of analogues of a related series of high-efficacy agonists to antagonists.

b. DISTRIBUTION AND BIOLOGICAL FUNCTION. DP receptors are perhaps the least ubiquitous of the prostanoid receptors. Only in American Type Culture Collection CCL 44 cells, a cell line derived from bovine embryonic trachea (Ito et al., 1990), have DP receptors been shown to exist as a homogeneous receptor population; in all other tissues in which they have been identified, they exist only in association with one or more other prostanoid receptor types. Therefore, it is difficult to study them in isolation. Fortunately, the available potent and selective DP receptor agonists and antagonists have proved valuable in the study of this receptor type.

DP receptors are distributed largely in blood platelets, vascular smooth muscle, and nervous tissue, including the central nervous system. There are also examples of DP receptors in gastrointestinal, uterine, and airway smooth muscle in some animal species (Coleman et al., 1990). Responses mediated by DP receptors are predominantly inhibitory in nature, e.g., inhibition of platelet aggregation and relaxation of smooth muscle and possibly inhibition of autonomic neurotransmitter release. However, DP receptors are associated with excitatory events in some afferent sensory nerves, where they can induce pain or, probably more correctly, hyperalgesia (Ferreira, 1983; Horiguchi et al., 1986). The distribution of DP receptors is highly species specific, e.g., human platelets appear to have a particularly rich population of inhibitory DP receptors (MacIntyre and Armstrong, 1987), whereas the platelets of most laboratory species appear to contain few if any DP receptors, and as far as uterine smooth muscle is concerned, DP receptors appear to be confined to the human (Sanger et al., 1982).

2. Ligand-binding studies. Few ligand-binding studies have been reported for DP receptors. PGD_2-specific binding sites have been identified in human platelet membranes, at which PGs of the E, F, and I series have substantially lower binding affinities but at which the DP receptor agonist, BW 245C, has high affinity (Cooper and Ahern, 1979; Town et al., 1983). Binding sites for [^{3}H]PGD_2 have also been identified in rat brain synaptic membranes (Shimizu et al., 1982).

3. Second-messenger studies. The evidence relating to DP receptors and second-messenger coupling is largely indirect. Simon et al. (1980) demonstrated that PGs D_2, E_2, and I_2 are approximately equipotent in stimulating

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TABLE 3
*Potencies of some DP receptor agonists and antagonists**

Agonists			Antagonists		
	Equieffective concentration (PGD_2 = 1)	References		pA_2	References
BW 245C	0.03–0.7	Town et al., 1983; Narumiya and Toda, 1985	BW A8685C	9.3	Giles et al., 1989
ZK110841	0.2–1.0	Thierauch et al., 1988; Ito et al., 1990	AH6809	6.0–6.6	Keery and Lumley, 1988; Ito et al., 1990
RS93520	1.0	Alvarez et al., 1991			

* Data obtained on human platelets, rabbit transverse stomach strip, rat peritoneal mast cells, and bovine embryonic trachea cells.

adenylate cyclase activity in human colonic mucosa. Because PGD_2 is only a very weak agonist at EP and IP receptors, this argues that, among others, DP receptors must be present in this preparation, coupling positively to adenylate cyclase, presumably via G_s. However, the demonstration by Ito et al. (1990) that activation of DP receptors in American Type Culture Collection CCL 44 cells (see above) results in an increase in levels of intracellular cAMP supports this association. Furthermore, several selective agonists exist for the DP receptor (Giles et al., 1989), and both of these and PGD_2 itself have been shown to bind to a specific DP receptor in platelets to cause an increase in cAMP formation (Gorman et al., 1977b; Schafer et al., 1979; Siegl et al., 1979a; Whittle et al., 1978), again suggesting that DP receptors can couple to G_s to stimulate adenylate cyclase (Halushka et al., 1989).

B. EP Receptors

1. Functional studies. a. SELECTIVE AGONISTS AND ANTAGONISTS. **i. EP_1 receptors.** Although sulprostone was first identified as a potent EP_1 receptor agonist, it is more potent at EP_3 receptors (Bunce et al., 1990). In fact, to date, there is no reported example of a highly selective EP_1 receptor agonist. Two compounds that have proven useful are 17-phenyl-ω-trinor PGE_2 (Lawrence et al., 1992) and iloprost (Sheldrick et al., 1988). The selectivity of 17-phenyl-ω-trinor PGE_2 for EP_1 receptors other than for EP_2 and EP_3 receptors is only about 10-fold, and thus, it is of limited value in the characterisation of EP receptors. In contrast, iloprost is more selective for EP_1 receptors over EP_2 and EP_3 receptors but is a partial agonist and, also, being a PGI_2 analogue, is a highly potent IP receptor agonist, being at least as potent as PGI_2 itself. As far as antagonists are concerned, there are a number of compounds with specific EP_1 antagonist activity, and at least some of these appear to be competitive receptor-blocking drugs, particularly SC-19220 and AH6809 (Sanner, 1969; Coleman et al., 1985). However, both of these compounds are weak. SC-19220 is also highly insoluble and possesses some local anaesthetic activity (Poll et al., 1989), and AH6809 has DP receptor-blocking activity and binds albumin avidly (Coleman et al., 1985). Quantitative data for some selective EP_1 receptor agonists and antagonists are summarised in table 4.

ii. EP_2 receptors. There are some EP receptor agonists that have proven useful in characterizing EP_2 receptors. The first identified EP_2 receptor agonist was the PGE_0 analogue, AY23626, but this compound was later found to possess relatively potent EP_3 receptor agonist activity (Coleman et al., 1987b). Another compound that has clearly demonstrable EP_2 receptor agonist activity is misoprostol, but like AY23626, it is also a potent EP_3 receptor agonist (Coleman and Humphrey, 1993). Both of these compounds are weak EP_1 receptor agonists and, therefore, can provide valuable information concerning EP_2 receptors in preparations devoid of EP_3 receptors. The only two compounds that have been reported to be selective for EP_2 receptors as opposed to the other three subtypes are butaprost (Gardiner, 1986) and AH13205 (Nials et al., 1993). However, both of these compounds suffer from low potency; thus, although they are selective for EP_2 receptors, both are between about 10- and 100-fold less potent than PGE_2, and their usefulness is limited. There are to date no reports of any compounds with EP_2 receptor-blocking activity. Quantitative data for some selective EP_2 receptor agonists are summarised in table 5.

iii. EP_3 receptors. There are many potent EP_3 receptor agonists, because they have been developed by various drug companies as potential antiulcer drugs (Collins, 1986). Misoprostol is an example of such a drug. However, many of these compounds also possess agonist activity at other EP receptors and even at other prostanoid receptors. Examples of these are rioprostil, M&B 28767, and nocloprost (Shriver et al., 1985; Lawrence and Jones, 1992; Täuber et al., 1988). Two compounds have been developed that are more selective for EP_3 receptors than the others, and these are enprostil and GR63799, both of which show a high degree of EP_3 receptor selectivity (Reeves et al., 1988; Bunce et al., 1990). These two compounds are not only highly selective but are also highly potent, both being at least 10-fold more potent than PGE_2 at EP_3 receptors. Despite the

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TABLE 4
*Potencies of some EP_1 receptor agonists and antagonists**

Agonists			Antagonists		
	Equieffective concentration (PGE_2 = 1)	References		pA_2	References
Sulprostone	4–6	Coleman et al., 1987a	SC-19220	5.2–5.6	Coleman et al., 1985, 1987a
Iloprost	~1†	Dong et al., 1986; Sheldrick et al., 1988	AH6809	6.4–7.0	Coleman et al., 1985, 1987a
17-Ph PGE_2	1	Lawrence et al., 1992			

* Data obtained on guinea pig isolated ileum and gastric fundus.
† Partial agonist.

TABLE 5
*Potencies of some EP_2 receptor agonists**

Agonist	Equieffective concentration (PGE_2 = 1)	References
Butaprost	6–30	Gardiner, 1986; Humbles et al., 1991
AH13205	30–100	Nials et al., 1993; Humbles et al., 1991
AY23626†	2–14	Coleman et al., 1987a
Misoprostol†	1–4	Coleman et al., 1988; Humbles et al., 1991
Rioprostil†	4	Coleman et al., 1988

* Data obtained on cat trachea and rabbit ear artery.
† Also potent EP_3 receptor agonist activity.

TABLE 6
Potencies of some EP_3 receptor agonists

Agonist	Equieffective concentration (PGE_2 = 1)	References
Enprostil	0.02–0.1	Reeves et al., 1988; Bunce et al., 1990; Strong et al., 1992
GR63799	0.1	Bunce et al., 1990
Sulprostone†	0.05–0.3	Coleman et al., 1988; Bunce et al., 1990; Strong et al., 1992; Lawrence et al., 1992
Misoprostol‡	02.–1.0	Reeves et al., 1988; Coleman et al., 1988; Bunce et al., 1990; Lawrence et al., 1992
Rioprostil‡	0.9–1.1	Reeves et al., 1988
M&B 28767	0.6	Lawrence et al., 1992
AY23626‡	3.0–7.7	Coleman et al., 1987a; Reeves et al., 1988

* Data obtained on guinea pig vas deferens, chick ileum, rat gastric mucosa, and rat adipocytes.
† Also has potent EP_1 receptor agonist activity.
‡ Also has potent EP_2 receptor agonist activity.

large amount of activity in this area of prostanoid chemistry, there are no reports of the discovery of any compound with EP_3 receptor-blocking activity. Quantitative data for some selective EP_3 receptor agonists are summarised in table 6.

iv. EP_4 receptors. The most recently identified of the subtypes of EP receptor is the EP_4 receptor (Coleman et al., 1994). There are currently no selective agonists for EP_4 receptors, but they were first identified in piglet saphenous vein, where prostanoid-induced smooth muscle relaxation was clearly mediated by an EP receptor but one at which selective agonists for EP_1, EP_2 and EP_3 receptors were weak or inactive. One further characteristic that distinguishes EP_4 receptors from the other three subtypes is their blockade by the TP receptor-blocking drugs, AH22921 and AH23848. Although the EP_4 receptors in piglet saphenous vein are blocked by these two TP antagonists, their potencies are low (pA_2 = 5.3 and 5.4, respectively), being at least 100-fold weaker than they are at TP receptors. AH23848, at least, has no antagonist activity at other EP receptors (Coleman et al., 1994).

b. DISTRIBUTION AND BIOLOGICAL FUNCTIONS. EP receptors mediate an impressive range of biological activities, including contraction and relaxation of smooth muscle, inhibition and enhancement of neurotransmitter release, inhibition of lipolysis, inhibition of gastric acid secretion, inhibition and enhancement of nonacid (water) secretion, inhibition of inflammatory mediator release, inhibition of immunoglobulin expression, immunoregulation, etc. (Coleman et al., 1990). It is partly because of the multitude of their biological actions that it first became obvious that there must be more than a single subtype of EP receptor. For example, looking at the effects of PGE_2 on smooth muscle, there are preparations, such as guinea pig trachea, where PGE_2 can cause contraction, relaxation, or both, depending on the conditions of the study; both responses appear to be mediated by EP receptors. This situation was clarified first by the use of the antagonists, SC-19220 and AH6809, that specifically blocked the contractions caused by PGE_2 but had no effect on the relaxations (Coleman et al., 1987a). This subdivision of EP receptors into two subtypes explained many otherwise puzzling observations; however, it soon became clear that more than two EP receptor subtypes were needed to account for all of the findings with PGE_2 and other, more selective EP receptor agonists. The first obvious inconsistency to the two-subtype system was contraction of the chick ileum, where the selective EP_1 receptor agonist, sulprostone, and the selective EP_2 receptor agonist, AY23626, both potently contracted the preparation, but neither

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SC-19220 nor AH6809 exhibited any antagonist activity (Coleman et al., 1987a). Subsequently, a number of agonists were discovered that had little or no agonist activity on preparations containing either EP_1 or EP_2 receptors but were highly potent in contracting chick ileum. The discovery of such compounds revealed that there were many preparations exhibiting "atypical" EP receptors; for example, guinea pig vas deferens and rat gastric mucosa, where PGE_2 caused inhibition of autonomic neurotransmitter release and inhibition of acid secretion, respectively (Coleman et al., 1987b; Reeves et al., 1988). It became apparent that these receptors represented a novel subtype of EP receptor, which were termed EP_3 (Coleman et al., 1987c). Additional functional studies by many different groups have now been published in support of the existence of these three subtypes of EP receptors, and their existence has gained widespread acceptance. It is now clear, however, that there also exists a fourth subtype of EP receptor, the EP_4 receptor (Coleman et al., 1994).

EP_1 receptors, although the first characterised of the EP receptor subtypes, do not appear to have a wide distribution, being most evident in smooth muscle from the guinea pig, where they exist in the trachea, the gastrointestinal tract, the uterus, and the bladder, where they mediate smooth muscle contraction. EP_1 receptors have also been demonstrated in at least some of these same tissues from rat and hamster. Although EP_1 receptors are more sparse in non-rodent species, they do exist, for example in dog gastric fundus (Coleman, 1987), bovine iris sphincter (Dong et al., 1986), and human myometrium (Senior et al., 1991). The tissue distribution of EP_1 receptors in mouse has been examined by Northern blot analysis (Watabe et al., 1993). Expression of EP_1 is generally low compared with other subtypes of EP receptor, although moderate expression was found in kidney and some was noted in lung. Sugimoto et al. (1994a,b,c) detected mRNA for the EP_1 receptor in the papillary collecting duct of mouse kidney.

EP_2 receptors more widespread and the responses mediated much more varied. They are widely distributed in smooth muscle, where they invariably mediate relaxation, on epithelial cells, where they mediate nonacid secretion, on inflammatory cells, such as mast cells and basophils, where they mediate inhibition of mediator release, and on sensory afferent nerves, where they mediate activation (Coleman et al., 1990). When examined by Northern blot analysis in mouse tissue, EP_2 receptors were found to be expressed most highly in ileum, followed by thymus, lung, spleen, heart, and uterus, in this order (Honda et al., 1993). EP_2 receptor mRNA in mouse kidney was specifically localised to the glomeruli (Sugimoto et al., 1994a,b,c).

Of the four subtypes, EP_3 receptors appear to be the most ubiquitous. They are present in smooth muscle of gastrointestinal, uterine, and vascular origin, where they mediate contraction, in autonomic nerves, where they mediate inhibition of neurotransmitter release, in adipocytes, where they mediate inhibition of lipolysis (Strong et al., 1992), in gastric mucosal cells, where they mediate inhibition of acid secretion (Reeves et al., 1988), and in renal medulla, where they mediate inhibition of water reabsorption (Sonnenburg and Smith, 1988). Their presence in the gastric mucosa has been exploited in the development of EP_3 receptor agonists as gastric antisecretory agents for the treatment of gastric ulcer and for the prevention of the side effects associated with long-term therapy with nonsteroidal anti-inflammatory drugs. They also appear to be present in human platelets, where they mediate a proaggregatory effect (Jones and Wilson, 1990), i.e., they do not induce aggregation in their own right but potentiate that to other aggregatory agents. EP_3 receptor mRNA is expressed very highly in kidney and uterus, and expression is also seen in stomach, thymus, spleen, lung, and brain (Sugimoto et al., 1992). Takeuchi et al. (1993) cloned the rat EP_3 receptor and examined its mRNA distribution in kidney by reverse transcription and polymerase chain reaction on microdissected nephron segments. Their results indicate that EP_3 mRNA is expressed in the thick ascending limbs of Henle's loop and in the collecting ducts in the cortex and medulla. The cellular distribution of the three EP_3 receptors in the kidney was examined by in situ hybridization by Sugimoto et al. (1994b); this work identified mRNA for EP_3 receptors in the tubules in the medulla, the distal tubules, and macula densa. The same authors also reported the distribution of the EP_3 receptor in nervous tissue. This receptor mRNA is expressed only in neurones and highly expressed in dorsal root ganglion and brain regions such as hippocampus, preoptic area, hypothalamus, maxillary body, locus coeruleus, and raphe nuclei (Sugimoto et al., 1994c).

There is currently little information concerning the distribution of EP_4 receptors, but after the first report of the existence of this receptor in piglet saphenous vein (Louttit et al., 1992a,b), evidence has been presented for the existence of what may be EP_4 receptors in rabbit jugular vein and saphenous vein, rat trachea, and hamster uterus (Lawrence and Jones, 1992; Yeardley et al., 1992; Lydford and McKechnie, 1993, 1994).

2. Ligand-binding studies. a. EP_1 RECEPTORS. Although in the 1970s many studies were performed on specific $[^3H]PGE_2$ binding to membranes from a range of different cells types, and the evidence from competition studies strongly pointed to these binding sites being EP receptors, there is very little information with which to identify the EP receptor subtype involved and none that any of them were EP_1 receptors (Coleman et al., 1990). Indeed, to date, there are still no reports of ligand-binding studies of native EP_1 receptors. However, such studies have been performed on recombinant EP_1 receptors from mouse (Watabe et al., 1993) and human (Funk et al.,

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1993). With the mouse receptors, expressed in Chinese hamster ovary cells, [^{3}H]PGE_2 had an affinity of 21 nM, this being displaced not only by unlabeled PGE_2 but also in approximately equipotent fashion by sulprostone, iloprost, and 17-phenyl-trinor PGE_2, all of which are essentially functionally equipotent with PGE_2 at EP_1 receptors. Furthermore, PGE_1, which is approximately 10-fold less potent than PGE_2 as an EP_1 receptor agonist, was one order of magnitude less potent than PGE_2 in displacing [^{3}H]PGE_2 from the recombinant EP_1 receptors; the selective EP_2 receptor agonist, butaprost, was virtually ineffective. Interestingly, the EP_1 receptor-blocking drug, AH6809, was virtually ineffective in displacing bound [^{3}H]PGE_2. This finding is difficult to explain in view of the established effectiveness of AH6809 in functional studies, although these have not been conducted in mouse tissues, and this may reflect species differences in ligand specificities of EP_1 receptors. With the human EP_1 receptors expressed in COS cells, [^{3}H]PGE_2 had an affinity of 1 nM and displacement characteristics similar to those observed with the recombinant mouse receptors in that the rank order of displacement was $PGE_2 > PGE_1 > PGF_{2\alpha} > PGD_2$, with butaprost being virtually ineffective. However, with the cloned human receptor, both AH6809 and SC-19220 were effective in displacing bound ligand, with potencies consistent with their affinity values for EP_1 receptors determined in functional studies.

b. EP_2 RECEPTORS. As with EP_1 receptors, it is by no means certain that any of the [^{3}H]PGE_2-binding sites described in early studies mentioned above correspond to EP_2 receptors. It is possible that the high-affinity sites ($K_d \simeq 1$ nM) identified by Kimball and Lauderdale (1975) and Rao (1976) in bovine corpus luteum were EP_2 receptors and were positively correlated with enhancement of adenylate cyclase activity. Beyond this, there have been no ligand-binding studies reported on native EP_2 receptors. There are reports of binding to recombinant EP_2 receptors from mouse (Honda et al., 1993) and human (An et al., 1993), both of which have been expressed in COS cells. Both of these receptors demonstrated high specific binding for [^{3}H]PGE_2 ($K_d \simeq 2$ and 11 nM), with much lower affinities for the other naturally occurring prostanoids, and for synthetic prostanoids selective for EP_1 and EP_3 receptors.

c. EP_3 RECEPTORS. In ligand-binding studies performed on membranes prepared from rat adipocytes and guinea pig and human myometrium and renal collecting tubule cells (Kuehl, 1974; Oien et al., 1975; Losert et al., 1979; Schillinger et al., 1979; Sonnenburg et al., 1990), there is evidence that the high-affinity ($K_d < 10$ nM) [^{3}H]PGE_2-binding sites identified are of the EP_3 subtype. First, on the basis of functional evidence, all of these tissues are known to contain EP_3 receptors, and second, two compounds with established EP_3 receptor agonist activity, sulprostone and AY23626, were shown to potently inhibit PGE_2 binding. It is interesting that the relative binding affinities of these two selective agonists relative to PGE_2 reflect their relative agonist potencies at EP_3 receptors (Coleman et al., 1990). However, Sewing and Beinborn (1990), in a study comparing binding affinities of a diverse range of prostanoids for the high-affinity PGE-binding sites in pig gastric mucosa with their abilities to inhibit pepsinogen secretion in the same tissue, found an EP_3 receptor-mediated response and an impressive correlation was obtained. A diagnostic feature of EP_3 receptors coupled to G_i is that guanine di- and trinucleotides actually decrease the K_d for ligand binding (Grandt et al., 1982; Watanabe et al., 1986, Sonnenburg et al., 1990).

Recombinant EP_3 receptors from mouse (Sugimoto et al., 1992), rat (Takeuchi et al., 1993), rabbit (Breyer et al., 1993), and human (Adam et al., 1994) have been expressed in COS cells, where they exhibit high affinities (K_d = 0.3 to 6.6 nM) for [^{3}H]PGE_2. In each case, in competition studies, the recombinant receptor exhibited a marked selectivity for PGE_2 over the other naturally occurring prostanoids or their synthetic mimetics. In each case, PGE_1 was as potent as PGE_2 in displacing radiolabeled ligand from the receptors, and in mouse, rabbit, and human homologues, potent, selective EP_3 receptor agonists, including M&B 28,767, sulprostone, and GR63799, were all potent competitors of [^{3}H]PGE_2 binding.

3. Second-messenger studies. a. EP_1 RECEPTORS. Creese and Denborough (1981) demonstrated that the PGE_2-induced contraction of guinea pig trachea is absolutely dependent on extracellular Ca^{2+}. Because PGE_2 is known to contract this preparation via EP_1 receptors (Coleman and Kennedy, 1985), this implicates a key role for extracellular Ca^{2+} in EP_1 receptor activation. However, in RCCT cells, PGE_2 and sulprostone both stimulate mobilization of Ca^{2+} from intracellular stores, and AH6809 causes about 50% inhibition of PGE_2-induced Ca^{2+} mobilization. Thus, Ca^{2+} mobilization in this system appears to be mediated, at least in part, via EP_1 receptors; PGE_2-induced Ca^{2+} mobilization was not blocked by pertussis toxin and does not require extracellular Ca^{2+}. Somewhat surprisingly, no changes in IP_3 formation were observed in response to treating RCCT cells with PGE_2. Thus, in the RCCT cell system, occupancy of EP_1 receptors appears to cause Ca^{2+} mobilization from intracellular stores via an IP_3-independent mechanism.

Studies with recombinant mouse and human EP_1 receptors (Watabe et al., 1993; Funk et al., 1993) also indicate that this receptor is involved in Ca^{2+} mobilization. Watabe et al. (1993) found that PGE_2 caused an increase in intracellular Ca^{2+} concentration in cells expressing the recombinant murine EP_1 receptor. This response consisted of two phases: a peak of about 30 s duration, followed by a slower but sustained increase of more than 3 min. The PI response evoked by this receptor was weak (about only 20% above control level) and

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occurred slowly, making it difficult to assess the contribution of the PI response to the rapid transient increase in free Ca^{2+} concentration in the cells. Changes in the intracellular cAMP level were negligible in the EP_1-expressing cells.

b. EP_2 RECEPTORS. The results of Simon et al. (1980), referred to above (see section II.A.3), provide indirect evidence for positive coupling of an EP receptor to adenylate cyclase, but more direct evidence has been provided by Hardcastle et al. (1982), in their demonstration of an association between EP_2 receptors and cAMP generation in enterocytes. The latter findings are supported and extended by Reimer et al.(1992), who examined a wide range of EP receptor subtype-selective agonists and the EP_1 antagonist, SC-19220. Similarly, Jumblatt and Peterson (1991) found an association between EP_2 receptor stimulation and cAMP generation in corneal endothelial cells. In both freshly isolated RCCT cells and in RCCT cells cultured for 4 to 5 days, PGE_2 acting at relatively high concentrations (ED_{50} = 500 nM) causes stimulation of cAMP formation (Sonnenburg and Smith, 1988). PGs of the E-series are the most effective in stimulating RCCT cell cAMP synthesis, indicating that this process is mediated via EP receptors. Despite this, the PGE_2 analogue sulprostone, which as indicated (section II.B.2.b) is not an effective agonist at EP_2 receptors, fails to stimulate cAMP formation in RCCT cells. These results imply that EP_2 receptors are coupled to adenylate cyclase presumably through G_s, at least in RCCT cells. Evidence that EP_2 receptors interact directly with a G_s is as follows. Depending on its concentration, PGE_2 can exert either stimulatory or inhibitory effects on cAMP formation by freshly isolated RCCT cells; furthermore, there are high- and low-affinity PGE_2-binding sites in these cells (Sonnenburg et al., 1990). In contrast to what is observed with freshly isolated RCCT cells, only the cAMP stimulatory effect of PGE_2 is observed with cultured RCCT cells; moreover, these cultured RCCT cells contain only one class of binding sites. Binding to this single class of sites is inhibited by guanine nucleotide derivatives. This latter finding argues that the EP_2 receptor of RCCT cells interacts with G_s.

In cells expressing the recombinant murine EP_2 receptor, PGE_2 increased the intracellular cAMP level without any change in inositol phosphate content (Honda et al., 1993). A threshold response was observed at 1 nM PGE_2, and a plateau was reached at 1 μM.

c. EP_3 RECEPTORS. The EP_3 receptor is an example of a promiscuous receptor that may couple to different second-messenger systems. Functionally, EP_3 receptors appear to be coupled to at least two different intracellular processes, one of which results in inhibition of autonomic neurotransmitter release, gastric acid secretion, and lipolysis, and another of which is involved in smooth muscle contraction (see section II.B.1.a.iii). The former are all responses classically mediated by inhibition of adenylate cyclase and the latter by increases in intracellular free Ca^{2+}, whether of intracellular or extracellular origin. In renal collecting tubule epithelia, occupancy of receptors having pharmacological properties of the EP_3 receptor causes inhibition of cAMP generation induced by treatment of the cells with arginine vasopressin (Sonnenburg and Smith, 1988). This receptor is apparently involved in vivo in inhibition of arginine vasopressin-induced water reabsorption (Smith, 1989). The activity of the renal EP_3 receptor is blocked by pertussis toxin, indicating that the receptor is coupled to a G_i (Sonnenburg et al., 1990); furthermore, this same receptor has been partially purified in association with a pertussis toxin-sensitive G-protein (Watanabe et al., 1986, 1991a). Thus, renal EP_3 receptors appear to be coupled to G_i and are involved in the inhibition of cAMP formation. EP_3 receptors associated with inhibition of hormone-induced cAMP synthesis are also present in stomach, where they are involved in the inhibition of histamine-induced acid secretion (Reeves et al., 1988), and in adipose tissue, where they inhibit epinephrine-induced lipolysis (Butcher and Baird, 1968; Strong et al., 1992). Both of these latter EP_3-mediated events are inhibited by pertussis toxin.

PGE_2 and an EP_3 agonist, M&B 28767, decreased forskolin-stimulated cAMP level in cells expressing the mouse EP_3 receptor. Interestingly, although PGE_2 and M&B 28767 have similar affinities for the recombinant EP_3 receptor, the potency of the M&B compound on native EP_3 receptor-containing preparations is more than two orders of magnitude higher than that of PGE_2. This difference appears to reflect the greater efficacy of the M&B compound, resulting in a more efficient catalysis by the M&B-EP_3 receptor complex in stimulation of the coupling G-protein than the PGE_2-EP_3 receptor complex, as examined by Sugimoto et al. (1993).

It should also be noted that an EP receptor is coupled via a pertussis toxin-insensitive G_q to phospholipase C in bovine adrenal glands to cause catecholamine release (Negishi et al., 1989, 1990; Yokohama et al., 1988). The identity of this receptor has not been established. It could be either an EP_1 receptor or the EP_{3D} receptor isoform recently cloned by Namba et al. (1993).

4. Molecular biology. a. EP RECEPTOR SUBTYPES. As discussed in more detail below, four EP_3 receptor isoforms were expressed from a bovine adrenal gland cDNA library by Namba et al. (1993) and designated EP_{3A}, EP_B, EP_C, and EP_D receptors when expressed in Chinese hamster ovary cells. EP_{3A} and EP_C receptors couple to G_i to induce inhibition of adenylate cyclase, EP_{3B} and EP_{3C} couple to G_s to increase cAMP, and EP_{3D} couples to G_q, in addition to G_i and G_s, to induce pertussis toxin-insensitive PI turnover and calcium mobilization.

As described in section II.B.1.a.iii, EP_3 receptors mediate a variety of actions. Although some of these actions such as the inhibition of vasopressin-induced water reab-

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sorption in kidney or histamine-induced gastric acid secretion and autonomic neurotransmitter release can be explained by EP_3-mediated inhibition of adenylate cyclase (Garcia-Perez and Smith, 1984; Chen et al., 1988; Sonnenburg and Smith, 1990), this mechanism cannot explain other EP_3 actions such as contraction of uterine and gastrointestinal smooth muscles, and it has been suggested that activation of EP_3 receptors causes calcium mobilization in these tissues (Coleman et al., 1987a,b,c; Goureau et al., 1992). Although the tissue distribution of each EP_3 isoform is not yet known, selected distribution could explain the various actions mediated by EP_3 receptors. Again, it is interesting that to date no responses to EP_3 receptor stimulation consistent with coupling to G_s and elevation of intracellular cAMP have been reported, although little work has been performed in the cow.

Sugimoto et al. (1992) and Watabe et al. (1993) used the mouse TP receptor cDNA as a probe and isolated two independent cDNA clones by cross-hybridization from a mouse lung cDNA library. The receptors encoded by both clones displayed specific $[^3H]PGE_2$ binding when expressed in cultured cells. Honda et al. (1993) then used the cDNA obtained by Sugimoto et al. (1992) as a probe and isolated a third clone that also encoded a protein that exhibited $[^3H]PGE_2$ binding. These three clones encode proteins of different sequences consisting of 365, 405, and 513 amino acid residues, respectively, that generate different signals on agonist binding. Analysis of the ligand-binding specificities as well as second-messenger generation suggested that these three clones correspond to the pharmacologically defined EP_3, EP_1, and EP_2 receptor subtypes, respectively. Genetic loci for the mouse EP_2 and EP_3 genes, *ptgerep2* and *ptgerep3,* respectively, were mapped to the centromeric region of chromosome 15 and the distal end of chromosome 3, respectively (Taketo et al., 1994). Ligand-binding properties of the recombinant EP receptors, as well as other prostanoid receptors as examined by their expression in cultured cells, are shown in table 7 and are discussed in section II.B.2.

b. EP_3 ISOFORMS. When Namba et al. (1993) used cDNA cloning of an EP receptor from a bovine adrenal gland cDNA library, they found that the EP_3 mRNA undergoes alternative splicing in this tissue to produce at least four EP_3 isoforms (EP_{3A}, EP_B, EP_C, and EP_D). The deduced amino acid sequences of these isoforms are identical from the amino terminus to the tenth intracellular amino acids after the seventh transmembrane domain but differ thereafter (fig. 2). Perhaps not surprisingly, because they share the same transmembrane and extracellular structures, the four isoforms showed almost identical ligand-binding specificities. Yet, as discussed in section II.B.3, these isoforms couple to different G-proteins to induce different signaling in the cells.

The presence of the EP_3 isoforms is not limited to the cow, because at least three EP_3 isoforms, $EP_{3\alpha}$, EP_β, and EP_γ, are also present in mouse (Irie et al., 1993), and the homologous splice variants are present in human and rabbit (Adam et al., 1994; Breyer et al., 1993). These isoforms show alternative splicing at the position identical with that found in the bovine variants. Among the mouse isoforms, $EP_{3\alpha}$ and EP_β couple to the same G-protein, G_i, and inhibit adenylate cyclase but are different in G-protein-coupling properties and sensitivity to agonist-induced desensitization; $EP_{3\alpha}$ couples to G_i more efficiently and is more sensitive to desensitization (Sugimoto et al., 1993; Negishi et al., 1993). The third isoform ($EP_{3\gamma}$) can couple to G_s in addition to G_i and, at higher agonist concentrations, tends to stimulate adenylate cyclase (Irie et al., 1993).

TABLE 7
Ligand-binding properties of the recombinant EP receptors

EP receptor subtype	K_d (nM)	Radioligand	Rank order of ligand*
EP_1	21	$[^3H]PGE_2$	PGE_2 > iloprost > PGE_1 >> $PGF_{2\alpha}$ > PGD_2 7-PhenylPGE$_2$ > sulprostone > M&B28767 > butaprost
EP_2	11	$[^3H]PGE_2$	PGE_2 = PGE_1 >> PGD_2, $PGF_{2\alpha}$, iloprost Misoprostol > M&B > sulprost, SC-19220, butaprost
EP_3	3	$[^3H]PGE_2$	PGE_2 = PGE_1 >> iloprost > PGD_2 > $PGF_{2\alpha}$ M&B28767 >>> butaprost, SC-19220 = 0

* The affinities of the various ligands for the receptors were determined in displacement experiments. The upper line shows the rank order of the "standard" prostanoids and the lower line that of various PGE analogues.

C. FP Receptors

1. Functional studies. a. SELECTIVE AGONISTS AND ANTAGONISTS. While $PGF_{2\alpha}$ is a potent FP receptor agonist, it is not very selective, having appreciable agonist activity at EP and TP receptors. However, two compounds in particular, fluprostenol and cloprostenol, both $PGF_{2\alpha}$ analogues synthesized by ICI in the 1970s, have proved to be at least as potent as the parent compound at FP receptors but have much reduced agonist activity at other prostanoid receptors (Dukes et al., 1974; Coleman, 1987). Of these compounds, fluprostenol is by far the most selective and in fact is probably the most selective agonist so far described at any prostanoid receptor. Although cloprostenol is a highly selective FP receptor agonist, it also has some, albeit weak, agonist activity at EP_3 receptors. Although there are various other potent FP receptor agonists, all of which are analogues of $PGF_{2\alpha}$, such as prostalene, fenprostalene, and tiaprost (Witherspoon et al., 1975; Jackson and Jessup, 1984), none is as selective as fluprostenol or cloprostenol. Although a few compounds have been reported to exhibit FP receptor-blocking activity, none has held up under close scrutiny. Thus, the N,N-dimethylamino and dimethylamido ana-

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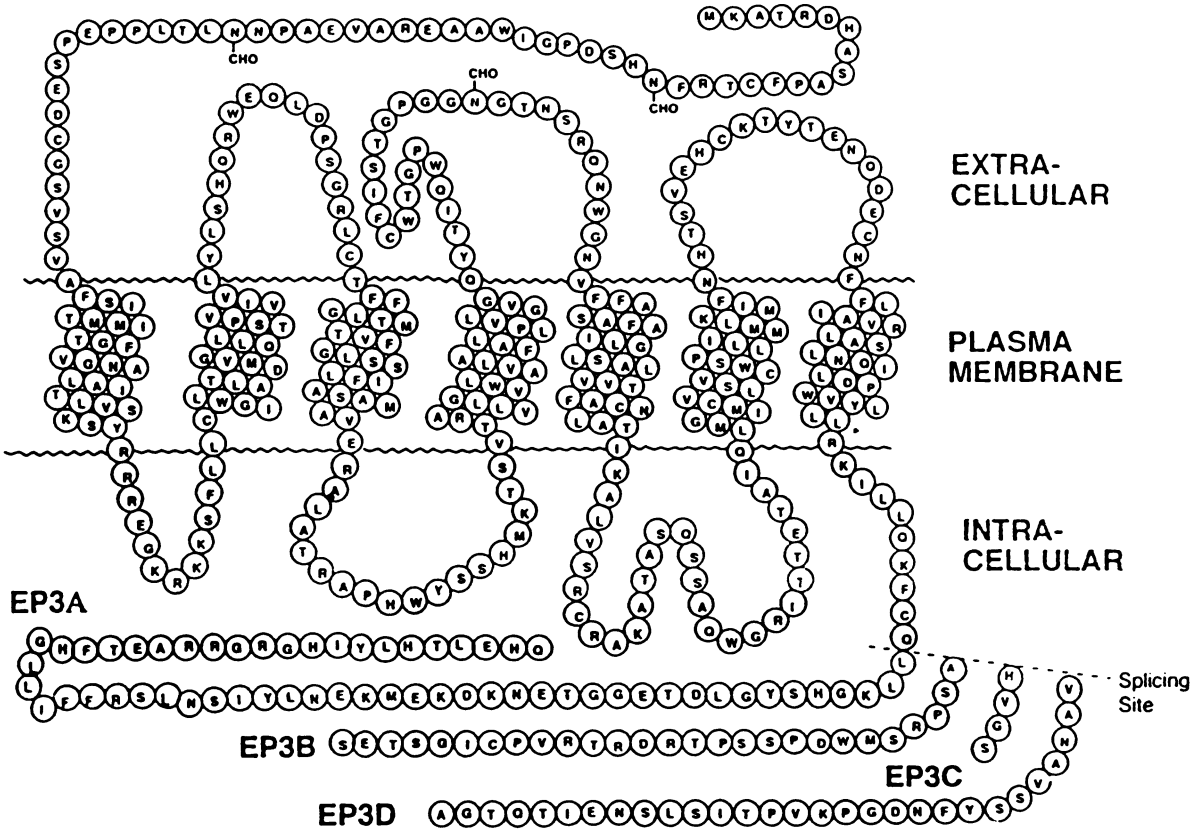

FIG. 2. Alternative splicing of the bovine EP_3 receptor. Structures of four isoforms of the bovine EP_3 receptor, EP_{3A}, EP_{3B}, EP_{3C}, and EP_{3D}, are shown.

logues of $PGF_{2\alpha}$ (Maddox et al., 1978) and an acetylenic analogue, K 10136 (Ceserani et al., 1979), have all been reported to block responses to $PGF_{2\alpha}$ on preparations containing FP receptors, but all three appear to be agonists (Coleman et al., 1990). In no study reported to date has any evidence for a subdivision of FP receptors emerged. This may be a reflection of the small number of selective FP agonists available and the absence of any antagonists. Quantitative data for some selective FP receptor agonists are summarised in table 8.

b. DISTRIBUTION AND BIOLOGICAL FUNCTIONS. FP receptors have been demonstrated to exist in a variety of different tissues from a range of different species. One tissue in which they are particularly prevalent is the corpus luteum, where they mediate luteolysis. Indeed, they appear to be present in the corpora lutea of all species investigated, including human. Because of their presence in this tissue, and their role in a fundamental stage of the female reproductive cycle, there was excitement initially in the potential of FP agonists as agents to control human fertility (Dennefors et al., 1983). However, this was never to be because in humans, unlike many other animal species, prostanoids are not central to the destruction of the corpus luteum, and $PGF_{2\alpha}$ and its analogues proved ineffective luteolytics. In a variety of other species, such as rat, hamster, cow, sheep, pig, and horse, $PGF_{2\alpha}$ and analogues are highly effective (Cooper et al., 1979) and have been marketed as agents to synchronize the oestrus cycles of farm animals to facilitate animal husbandry.

TABLE 8
*Potencies of some FP receptor agonists**

Agonist	Equieffective concentration ($PGF_{2\alpha}$ = 1)	References
Fluprostenol	0.2–1.0	Dong and Jones, 1982; Coleman, 1983; Woodward et al., 1990
Cloprostenol	0.3–0.5	Coleman, 1983
Prostalene	0.7–2.7	Coleman, 1983

* Data obtained on dog and cat iris sphincter and Swiss 3T3 cells.

In some rodents, but not guinea pig, and in humans, there are contractile FP receptors on the myometrium (Whalley and White, 1980; Senior et al., 1992). Interestingly, it is reported that in dogs, far from being the innocuous agents that they are in farm animals, FP agonists are lethal. In both dogs and cats, it is probably relevant, therefore, that there are FP receptors on airway smooth muscle, where they mediate contraction (Coleman, 1987); FP receptors have not been reported in the airways of any other species.

One tissue that has proved most useful in the study of FP receptors is the iris sphincter muscle from both cat and dog, where FP receptors mediate contraction (Coleman, 1983, 1987). In this tissue, FP receptors exist as homogeneous populations, and thus, much of the func-

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tional work on FP receptors has been carried out on iris sphincter. The presence of FP receptors in ocular tissue has had important pharmacological consequences because $PGF_{2\alpha}$ and various analogues such as latanoprost (Camras et al., 1992) have proven effective in lowering intraocular pressure in various species, including human, and are used to treat glaucoma. However, the exact site of action of these prostanoids in the eye to produce this effect is a matter of debate.

RNA blot analysis of mouse FP receptors showed two major hybridization bands at 2.3 and 6 kb, and, as expected, the highest expression was observed in the pregnant mouse ovary. Expression was also prominent in kidney and significant in lung, heart, and stomach. In situ hybridization analysis in ovary showed that the mRNA expression was observed exclusively in the large luteal cells of corpus luteum, whereas no labeling was found in any stages of ovarian follicle. This distribution of the receptor expression appears consistent with the known actions of $PGF_{2\alpha}$ including its effects on luteolysis (Horton and Poyser, 1976), contraction of mesangial cells in kidney glomerulus (Mené et al., 1987), and bronchoconstriction (Wasserman, 1975).

2. Ligand-binding studies. A large number of studies have been performed on PGF-specific binding sites in membranes of corpora lutea from various species, including rat (Wright et al., 1979), rabbit (Losert et al., 1979), sheep (Kuehl, 1976; Hammarström et al., 1976), cow (Kimball and Lauderdale, 1975; Powell et al., 1976; Lin and Rao, 1978), and horse (Kimball and Wyngarden, 1977; Lin and Rao, 1978), preparations known to contain functional FP receptors. These all show high-affinity (<10 nM) binding for $[^3H]PGF_{2\alpha}$ and highly selective displacement by unlabeled $PGF_{2\alpha}$, and also in some studies by the potent and highly selective FP receptor agonist, fluprostenol (Kimball and Lauderdale, 1975; Kimball and Wyngarden, 1977; Lin and Rao, 1978; Wright et al., 1979). Significantly, the relative potencies of the prostanoids studied in inhibiting $[^3H]PGF_{2\alpha}$ binding to the luteal binding sites are remarkably similar to their relative agonist potencies at FP receptors (Coleman et al., 1990).

When expressed in COS cells, a recombinant FP receptor bound $[^3H]PGF_{2\alpha}$ with a K_d of 1.32 nM, and this $[^3H]PGF_{2\alpha}$ binding was displaced by unlabeled PGs in the order of $PGF_{2\alpha} = 9\alpha,11\beta\text{-}PGF_2 > PGF_{1\alpha} > PGD_2 > STA_2 > PGE_2 >$ iloprost. The affinity and specificity of this binding are in good agreement with the FP receptor characterized previously in corpus luteum membranes (Powell et al., 1974).

3. Second-messenger studies. FP receptor-mediated luteolysis is associated with an elevation of intracellular free Ca^{2+}, which appears to be of intracellular origin (Behrman et al., 1985). Furthermore, Raymond et al. (1983) have shown that $PGF_{2\alpha}$ induces PI turnover in isolated luteal cells. As noted in section II.C.1.b, $PGF_{2\alpha}$ derivatives have been used to lower intraocular pressure in the treatment of glaucoma (Camras et al., 1989; Woodward et al., 1989). The order of potency of various prostanoids in lowering intraocular pressure is the same as that for contraction of the cat iris sphincter and for activation of Ca^{2+} mobilization in Swiss mouse 3T3 cells (Woodward et al., 1990; Woodward and Lawrence, 1994) where $PGF_{2\alpha}$ acts as a mitogen (Jimenez de Asua et al., 1981; Nakao et al., 1993). The effect of $PGF_{2\alpha}$ to induce Ca^{2+} mobilization in murine fibroblasts occurs in conjunction with formation of IP_3 and is pertussis toxin insensitive (Gusovksy, 1991; Nakao et al., 1993; Quarles et al., 1993). These findings suggest that FP receptors can interact with a member of the G_q protein family to activate phospholipase C, leading ultimately to an IP_3-mediated mobilization of Ca^{2+} from intracellular pools. However, there also appears to be a secondary phase of Ca^{2+} release by $PGF_{2\alpha}$-treated murine fibroblasts that is likely due to extracellular Ca^{2+} entry (Nakao et al., 1993).

$PGF_{2\alpha}$ (1 to 1000 nM) added to COS cells transfected with a recombinant murine FP receptor evoked a concentration-related formation of inositol-1,4,5-trisphosphate, and the response reached a plateau of 180% of the control at 1 μM (Sugimoto et al., 1994a,b,c). These results indicate that the recombinant receptor also couples to activation of phospholipase C, resulting in a consequent Ca^{2+} mobilization.

4. Molecular biology. Sugimoto et al. (1994a,b,c), using bovine corpus luteum and mouse ovary, isolated a cDNA for the mouse FP receptor by homology-based polymerase chain reaction and cross-hybridization. The mouse FP receptor is a rhodopsin-type protein of 366 amino acids homologous to other prostanoid receptors. High homology is observed to the mouse TP receptor and EP_1 receptor, 39.3 and 39.8% in total sequences, respectively.

D. IP Receptors

1. Functional studies. a. SELECTIVE AGONISTS AND ANTAGONISTS. PGI_2 itself has been tested as an inhibitor of platelet aggregation for the treatment of thrombotic diseases and as a vasodilator for the treatment of vascular occlusive diseases. The chief problems with PGI_2 itself are that it is chemically unstable, and thus, has too short a duration of action, and that it does not discriminate between platelet and vascular IP receptors. Both PGE_1 and its 6-keto analogue are moderately potent IP receptor agonists, which are both more stable than PGI_2, but suffer from the same vascular side effects. It is possible that PGI_2 may also suffer from limited selectivity of action, but because of its short duration of action, nonvascular side effects are not limiting. A great deal of effort has been directed toward trying to identify more stable and more platelet-selective analogues. Although increased stability was relatively simple to achieve in all of the early analogues, it was at the expense of potency, and simple carbon analogues of PGI_2, such as carbacy-

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clin, are considerably weaker IP agonists than the parent compound. The first compound to combine chemical stability with high IP receptor agonist potency was the Schering compound, iloprost (Schrör et al., 1981), which is at least as potent as PGI_2 at IP receptors but is far more stable and has an extended duration of action in vivo (Skuballa et al., 1985). However, like the parent compound, iloprost fails to distinguish between platelet and vascular IP receptors, and therefore, anti-platelet activity is at the expense of profound vasodepression. Although in most respects iloprost is more IP receptor selective than is PGI_2, particularly in their respective EP_3 and TP receptor agonist activities, it is less selective in terms of EP_1 receptor agonist activity. At EP_1 receptors it is approximately equipotent with PGE_2, albeit a partial agonist, and is at least 20-fold more potent than PGI_2 (Sheldrick et al., 1988). A further development from Schering was cicaprost (Stürzebecher et al., 1985), which is slightly more potent than iloprost as an IP receptor agonist but with little or no agonist activity at any other prostanoid receptor at which it has been tested. There are now many other PGI_2 analogues that are potent IP receptor agonists, but none has been tested in as comprehensive a way as iloprost and cicaprost. One other compound worthy of note is octimibate (Merritt et al., 1991), a compound with little obvious structural resemblance to PGI_2, yet one that exhibits modest agonist activity at primate IP receptors. Interestingly, this compound is much weaker at IP receptors from other species, which is suggestive of species variability among IP receptors. However, even with octimibate, there is no indication of any difference between vascular and platelet IP receptors within a species. Quantitative data for some selective IP receptor agonists are summarised in table 9.

Although an enormous amount of chemistry has been undertaken to make analogues of PGI_2, no IP receptor-blocking drug has yet been identified. One compound of interest is (5Z)-6a-carba-PGI_2 (Corsini et al., 1987), which behaves as a full IP receptor agonist on human platelets but which is only a partial agonist on rat arterial myocytes and rabbit isolated mesenteric artery. Therefore, this compound appears to possess a low efficacy at IP receptors and may represent a starting point toward the development of IP receptor-blocking drugs. Finally, one compound reported to be an IP receptor-blocking drug is another PGI_2 analogue, FCE 22176 (Fassina et al., 1985). This compound antagonises the contractile effects of PGI_2 on guinea pig trachea, but this preparation does not contain IP receptors, contraction being mediated by EP_1 and TP receptors (Coleman and Kennedy, 1985). It is more likely, therefore, that FCE 22176 is an EP_1 receptor-blocking drug.

TABLE 9
*Potencies of some IP agonists**

Agonist	Equieffective concentration (PGI_2 = 1)	References
Carbacyclin	3.5–30	Whittle and Moncada, 1985; Armstrong et al., 1989
Iloprost†	0.4–3.5	Casals-Stenzel et al., 1983; Stürzebecher et al., 1985; Humbles et al., 1991; Armstrong et al., 1989
Cicaprost	0.05–1.2	Stürzebecher et al., 1985; Armstrong et al., 1989; Humbles et al., 1991
Octimibate	29	Merritt et al., 1991

* Data obtained on human and rat platelets and bovine coronary artery.

† Also a potent EP_1 receptor agonist (see table 3).

Despite considerable effort directed toward developing platelet-selective analogues of PGI_2, there is no clear example of success, and there is no convincing evidence that IP receptors can be subclassified; the only differences that exist probably result from species variants of IP receptor rather than from true subtypes.

b. DISTRIBUTION AND BIOLOGICAL FUNCTIONS. PGI_2 is synthesised primarily by the vascular endothelium, and it plays an important inhibitory role in local control of vascular tone and platelet aggregation (Moncada, 1982). It is not surprising, therefore, that IP receptors are localised in both blood platelets and vascular smooth muscle (Oliva and Nicosia, 1987). However, it has been observed that, whereas arterial homogenates appear to generate substantial amounts of PGI_2, venous homogenates do not, generating, instead, PGE_2 (Skidgel and Prinz, 1978). It is interesting, therefore, that vascular IP receptors appear to be confined to the arterial side of the circulation, and although venous smooth muscle does possess inhibitory prostanoid receptors, they are primarily of the EP type (Coleman et al., 1990).

IP receptors are also found in other tissues, particularly in sensory afferent nerves, where they mediate an excitatory response (Birrell and McQueen, 1993). PGI_2 is a potent hyperalgesic agent, and IP receptors have been implicated in this action.

Northern blot analysis using the IP receptor cDNA revealed that its mRNA is most abundantly expressed in thymus, followed by spleen, heart/aorta, and lung, in this order (Namba et al., 1994). In the thymus, this receptor is expressed almost exclusively in the medulla, suggesting a novel immunomodulatory role for this prostanoid.

2. Ligand-binding studies. IP receptors are widely distributed on blood platelets, vascular smooth muscle, and nerve cells, and binding studies have been performed on membrane preparations from each (Schafer et al., 1979; Siegl et al., 1979b; Schillinger and Losert, 1980; Schillinger and Prior, 1980; Blair and MacDermot, 1981; Town et al., 1982; Leigh et al., 1984; Lombroso et al., 1984), variously using [^{3}H]PGE_1, [^{3}H]PGI_2, and [^{3}H]iloprost as radioligand. Binding studies have also been performed on guinea pig lung homogenates, using [^{3}H]PGI_2 as ligand (MacDermot et al., 1981). In each case, the radioligand had high affinity (<10 nM), and in competition studies, a clear rank order of competitive potency was obtained: iloprost ≃ PGI_2 > PGE_1 > PGD_2, PGE_2, $PGF_{2\alpha}$,

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with PGE_1 being of the order of 10-fold less potent than PGI_2 (Coleman et al., 1990). This profile corresponds to that associated with functional activity at IP receptors.

With the murine IP receptor expressed in cultured Chinese hamster ovary cells, [^{3}H]iloprost binds with a K_d of 4.5 nM, and this binding is inhibited by various PGI analogues and other prostanoids in the order: cicaprost > iloprost > PGE_1 > carbacyclin ≫ PGD_2, STA_2, PGE_2 > $PGF_{2\alpha}$. Thus, the affinity of iloprost and the specificity of the binding fo the recombinant mouse IP receptor agree well with the previous characterization of the receptor in platelets and other sources (Leigh et al., 1984; Armstrong et al., 1989; Hashimoto et al., 1990).

3. Second-messenger studies. As discussed in section II.D.1.b, IP receptors are found principally in the arterial vasculature and circulating platelets, where along with TP receptors they participate in the reciprocal regulation of cAMP levels (Gorman et al., 1977a, 1978; Schafer et al., 1979; Siegl et al., 1979a,b; Halushka et al., 1989). IP receptors appear to couple to adenylate cyclase via G_s (Siegl et al., 1979b; Hashimoto et al., 1990; Ito et al., 1992).

Although cAMP generation is generally regarded as the sole signal transduction system for IP receptors, there have been several reports of PGI_2 and its analogues inducing increases in intracellular [Ca^{2+}] and evoking smooth muscle contraction (Whittle et al., 1979; Watanabe et al., 1991b; Lawrence et al., 1992; Vassaux et al., 1992). Although these findings suggest the possibility that IP receptors may couple through calcium mobilisation, it is by no means certain that all of these effects are actually mediated by IP receptors and, even if they are, that the "excitatory effect" does not result from the release by the IP agonist of another mediator.

The recombinant IP receptor from mouse, when expressed in Chinese hamster ovary cells, stimulates adenylate cyclase. The EC_{50} of iloprost in this response was 0.1 nM, which is 10-fold lower than that found for the p-815 cells, from which the IP receptor was cloned. This suggests that the receptor-G-protein coupling is more efficient in the Chinese hamster ovary cell system. In addition to this well-known effect on adenylyl cyclase, the recombinant receptor mediated phosphatidylinositol turnover at the higher iloprost concentrations, with an EC_{50} of 100 nM; at 1 μM iloprost, IP_3 formation was observed 30 s after the agonist addition and reached a maximum about 3-fold over the control at 2 min.

4. Molecular biology. Namba et al. (1994) isolated a cDNA for the mouse IP receptor by polymerase chain reaction-based homology screening from the library of mouse mastocytoma p-815 cells, which express a high amount of the receptor. It is a protein of 417 amino acids with a calculated M_r of 44,722, and the amino acid sequence in the transmembrane domains shows the highest homology, 39%, to the EP_2 receptor; the homology to other receptors is 32, 28, and 32% to EP_3, EP_1, and TP, respectively.

There have been some concerns regarding the existence of subtypes or isoforms of the PGI receptor. However, there has been no evidence for the presence of homologous molecules or alternatively spliced variants of the cloned receptor.

E. TP Receptors

1. Functional studies. a. SELECTIVE AGONISTS AND ANTAGONISTS. The situation with regard to the availability of TP receptor-active agents is unlike that for other prostanoid receptors in that there are few selective agonists, but many antagonists, and these are of a wide variety of chemical types. The only selective TP receptor agonists that have been at all widely used are the 9,11-epoxymethano and 9,11-methanoepoxy analogues of PGH_2, U44069 and U46619 (Malmsten, 1976). Of these two, U46619 is the more selective, and the most frequently used, and appears to have an agonist profile similar to that of TxA_2 itself (Coleman et al., 1981b). Although other TP receptor agonists [e.g., 9,11-azo PGH_2 (U-57093), $PGF_{2\alpha}$ acetal and EP 011] have been developed and used experimentally, they are not only less selective but in most cases also less potent (Corey et al., 1975; Portoghese et al., 1977; Wilson and Jones, 1985). However, there are exceptions, such as EP171, SQ 26655, I-BOP, and STA_2 (Sprague et al., 1985; Wilson and Jones, 1985). Of these compounds, EP171 has a unique profile, being exceptionally long acting.

The many antagonists that exist are of a wide range of structural types, some more or less closely related to TxA_2, some loosely prostanoid in nature, and others that are of quite different structural origin. Some of the earliest TP receptor-blocking drugs identified on blood platelets were TxA_2 analogues, such as 9,11-azaprosta-5,13-dienoic acid, 9,11-epoxyimino-5,13-dienoic acid, carbathromboxane, and pinane TX (Gorman et al., 1977a; Fitzpatrick et al., 1978; Nicolaou et al., 1979), but these compounds behaved as agonists on vascular preparations. This probably does not constitute evidence for receptor subtypes but, rather, reflects the fact that these compounds are partial agonists, and the TP receptors in smooth muscle appear to be more efficiently coupled than those in platelets. Other compounds that, although broadly prostanoid in nature, are less closely related to TxA_2 include the 7-oxabicyclo [2.2.1] heptane analogues, such as SQ 29548 (Sprague et al., 1980), AH19437, AH23848, and vapiprost (Coleman et al., 1981a; Brittain et al., 1985; Lumley et al., 1989), EP 045 and EP 092 (Jones and Wilson, 1980; Armstrong et al., 1985), and ICI 192605 (Brewster et al., 1988). In addition to such prostanoid-related compounds, there are others that bear no obvious structural resemblance to the prostanoids but, nevertheless, are potent TP receptor-blocking drugs. Examples of such compounds are trimetoquinol, the ben-

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zylsulfonamide, daltroban, the indole-2-propanoic acid, L-655240 (Hall et al., 1987; Lefer, 1988), and BAY u 3405 (Rosentreter et al., 1989). Each of these compounds is a relatively highly potent antagonist, with pA_2 values in the range 7.0 to 9.0, but for only some is there any information regarding their TP receptor selectivity. Thus, it is clear that only AH19437, AH23848, vapiprost, EP 045, EP 092, ICI 192605, and BAY u 3405 are without antagonist activity at DP, EP_1, EP_2, EP_3, FP, or IP receptors (Coleman and Humphrey, 1993), although AH23848 does have some additional weak antagonist activity at EP_4 receptors (Coleman et al., 1994). Quantitative data for some selective TP receptor agonists and antagonists are summarised in table 10.

b. DISTRIBUTION. In many respects, TP receptors are the counterpart of IP receptors, and in many tissues these two types of receptor demonstrate a "yin-yang" relationship. Thus, TP receptors are widely distributed in vascular smooth muscle and platelets and invariably mediate excitatory activity (i.e., vasoconstriction and platelet aggregation; Malmsten, 1976; Coleman et al., 1981b; MacIntyre, 1981). However, the distribution of TP receptors does not strictly reflect that of IP receptors, because there is no evidence for the presence of TP receptors in nerves, either afferent or efferent. In addition, unlike IP receptors, TP receptors invariably appear to be present in airway smooth muscle (Coleman and Kennedy, 1985; Humphrey et al., 1986; Coleman, 1987; Coleman and Sheldrick, 1989), although not necessarily at all levels of the bronchial tree. In contrast, airway smooth muscle appears to be devoid of IP receptors. Even in vascular smooth muscle, the distributions of TP and IP receptors do not totally correspond, because TP receptors appear to exist in all vascular smooth muscle so far examined, irrespective of their arterial or venous origin. Also, unlike IP receptors, TP receptors appear to be present in all vascular tissue and actually play a key physiological role in the closure of umbilical vessels at birth. This is one of the few examples of a physiological role for TP receptors, most other actions appearing to be pathological or pathophysiological in nature. TP receptors do not appear to be widely distributed in cells other than smooth muscle and platelets, but they are present in myofibroblasts (Coleman et al., 1989) and may well play a role in wound healing and scar formation. They also exist in mesangial cells in the kidney, where they mediate an increase in filtration rate (Scharschmidt et al., 1986), and in epithelium of the gastrointestinal tract, where they mediate an increase in secretion (Bunce and Spraggs, 1987; Clayton et al., 1988).

TABLE 10

*Potencies of some TP receptor-blocking drugs**

Antagonist	pA_2	References
AH19437	5.9–6.6	Coleman et al., 1981a,b
AH23848	7.8–8.3	Brittain et al., 1985
GR32191 (vapiprost)	8.2–8.8	Lumley et al., 1989
EP 045	5.9–7.1	Jones et al., 1981
EP 092	7.2–8.4	Armstrong et al., 1985
SQ 29548	7.8–9.1	Ogletree et al., 1985
ICI 192605	8.2–8.4	Brewster et al., 1988
L-655240	8.0–8.4	Hall et al., 1987
BAY u 3405	8.1–8.9	McKenniff et al., 1991
S-145	8.5–9.0†	Hanasaki and Arita, 1988
BM 13505 (daltroban)	6.7–7.9	Lumley et al., 1989

* Data obtained on platelets and vascular smooth muscle from a range of species.

† K_i values from binding experiments on platelets from rat, rabbit, and human.

Recently, Namba et al. (1992) examined the tissue distribution of TP receptor mRNA by Northern blot analysis in various mouse tissues. This study revealed that the TP receptor is expressed most abundantly in thymus, followed by spleen, lung, kidney, heart, and uterus, in that order. Traces of TP receptor mRNA were observed in brain. In a similar analysis of human tissues (Hirata et al., 1991), placenta and cultured megakaryocytic leukaemia cells showed higher expression than lung. Thus, along with placenta and platelet precursor cells, thymus is one of the richest tissues in receptor expression. Ushikubi et al. (1993) examined a thymic cell population expressing the receptor by means of radioligand binding and found that the thymic lymphocytes express TP receptors at a density comparable to that found in human platelets. TP receptors are most highly expressed in immature thymocytes, such as $CD4^-8^-$ and $CD4^+8^+$ cells, but the numbers decrease during T-cell development. They also found that the addition of a TP agonist induced apoptotic cell death of these immature thymocytes and that this action was antagonized by a TP receptor antagonist. These results, together with the finding that TX synthase is rich in dendritic cells and macrophages in thymus (Nüsing et al., 1990; Homo-Delarche et al., 1985), led these authors to suggest that TXA_2 is released from these stromal cells and acts on thymocytes under some physiological conditions. Thus, in addition to its well-known actions in cardiovascular and respiratory systems, TP receptors may play a role in thymocyte differentiation and development.

2. Ligand-binding studies. Ligand-binding studies with TP receptors are very much more numerous than those with any of the other prostanoid receptors, and there has also been a greater variety of ligands, both agonist and antagonist, used. Such studies have been performed predominantly on membrane preparations from platelets, but vascular and bronchial smooth muscle have also been used. Agonist ligands include [^{3}H]U44069 (Armstrong et al., 1983), [^{3}H]U46619 (Kattelman et al., 1986), and [^{125}I]-BOP (Morinelli et al., 1990), the latter having a particularly high affinity of 2 nM, compared with values of about 100 nM for the other two compounds. Antagonist ligands used in earlier studies were [^{3}H]13-azaprostanoic acid (Hung et al., 1983) and ^{125}I-13-aza,16-*p*-hydroxyphenylpinane TxA_2 (Mais et al., 1985a,b; Halushka et al., 1986), but both of these compounds have relatively

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low affinities, of the order of 100 and 20 nM, respectively. More recently, a variety of radiolabeled TP receptor-blocking drugs have been developed as ligands, and these have very much higher affinities for TP receptors; examples of these ligands are [^{3}H]SQ 29548 (Hedberg et al., 1988), [^{3}H]GR32191B (Armstrong et al., 1993), and [^{125}I]S-145 (Kishino et al., 1991), all of which have K_d values of <10 nM; for [^{125}I]S-145, Kishino et al. (1991) reported K_d values of 0.2 and 0.4 nM, respectively, at TP receptors on membranes prepared from platelets and vascular smooth muscle.

Ligand-binding properties of recombinant TP receptors have been examined following receptor expression in cultured COS cells. The human and mouse receptors showed specific binding of the selective TP receptor ligand, [^{3}H]S-145, with a K_d of 1.2 and 3.3 nM, respectively; this binding is displaced selectively by various TP analogues in the order of S-145 > ONO-3708 > STA_2 > U46619. Other PGs, such as PGD_2, also displace the binding, but their potencies are more than two orders of magnitude less than those of the above compounds.

3. Second-messenger studies. Studies of the relationship between TP receptor agonists and antagonists and second-messenger generation have been conducted largely on platelets and vascular smooth muscle cell preparations. In the case of platelets, there appear to be two separable effects with different pharmacologies. S-145 and U44619 both cause an initial platelet shape change, but only U44619 causes platelet aggregation (Arita et al., 1989; Hanasaki and Arita, 1988); in fact, S-145 antagonises platelet aggregation mediated through TP receptors. S-145 causes an increase in the cytosolic Ca^{2+} concentration which is independent of extracellular Ca^{2+} (Nakano et al., 1988) and which does not involve changes in IP_3 levels (Arita et al., 1989), suggesting that platelet shape change involves mobilization of Ca^{2+} from intracellular stores via an IP_3-independent process. Platelet aggregation itself involves mobilization of Ca^{2+} from intracellular pools but in association with activation of phospholipase C and consequent production of IP_3 (Arita et al., 1989; Brass et al., 1987; Pollock et al., 1984; Sage and Rink, 1987; Siess et al., 1986; Watson et al., 1985); platelet aggregation also requires extracellular Ca^{2+}. In platelets, the effects of U44619 are not inhibited by pertussis toxin (Brass et al., 1987). This finding, in combination with results indicating that TP receptor occupancy leads to phospholipase C activation, suggest that platelet TP receptors are coupled in part to a pertussis toxin-insensitive G-protein of the G_q family. In support of this suggestion, Shenker et al. (1991) showed that antibodies specific for the G_q family block U44619-induced phospholipase C activity; moreover, Knezevic et al. (1993) showed that TP receptors purified by affinity chromotagraphy are associated with two G-proteins; one is a G_q (M_r 42,000) and another has a higher M_r (85,000). Overall, these studies suggest that platelet TP receptors couple directly to G_q to cause phospholipase C activation, IP_3-dependent Ca^{2+} mobilization, and activation of protein kinase C through diglyceride formation and further that TP receptors couple to a second G-protein. It is not clear whether coupling to the M_r 85,000 G-protein is involved in IP_3-independent Ca^{2+} mobilization and/or a Ca^{2+} channel that mediates the entry of extracellular Ca^{2+}.

U44619 is well-known to cause contraction of vascular smooth muscle strips (Dorn et al., 1992; Yamagishi et al., 1992). Treatment of cultured smooth muscle cells with U44619 causes an increase in IP_3, the mobilization of intracellular Ca^{2+}, and phosphorylation of myosin light chain kinase (Dorn et al., 1992; Miki et al., 1992; Yamagishi et al., 1992). TP receptor-blocking drugs inhibit the Ca^{2+} mobilization caused by U44619. These results suggest that smooth muscle contraction occurring in response to agonists involves interaction with a G-protein coupled to phospholipase C; the parallel to second-messenger generation associated with TP receptor-mediated platelet aggregation is obvious. Vascular endothelial cells also contain TP receptors, and treatment of bovine aortic endothelial AG4762 cells with U44619 causes increases in intracellular Ca^{2+} concentrations. The mechanism underlying TP receptor-mediated Ca^{2+} by endothelial cells is not yet known.

Signal transduction examined by expression of the recombinant murine TP receptors revealed that when stimulated by an agonist, the receptor evoked PI turnover and subsequent Ca^{2+} release, as suggested by studies with cells and membranes containing the native TP receptor (Arita et al., 1989).

4. Molecular biology. Ushikubi et al. (1989), using a TP receptor antagonist, S-145, as an affinity ligand, purified the TP receptor about 9000-fold to apparent homogeneity from solubilized membranes from human blood platelets. Based on partial amino acid sequences obtained from the purified protein, Hirata et al. (1991) cloned a cDNA for the human TP receptor from MEG-01 human megakaryocytic leukaemia cell and human placenta cDNA libraries. A mouse homologue was subsequently isolated by polymerase chain reaction and hybridization screening (Namba et al., 1992). The human and mouse TP receptors consist of 343 and 341 amino acids, respectively, and are 76% identical in the overall sequences. The receptors have an N-terminal extracellular portion of <30 amino acids, and the fourth and 16th asparagine in this region are glycosylated as evidenced by peptide sequencing of the purified protein. Transmembrane segments consist mainly of hydrophobic amino acids, and the three-dimensional structure model based on the sequence suggests that these hydrophobic amino acids form a hydrophobic pocket for the hydrophobic ring structure of TxA_2 (Yamamoto et al., 1993). The cytoplasmic loops are short, and there are two conserved potential protein kinase C phosphorylation sites in the second cytoplasmic

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loop, which together with several serine and threonine residues in the C terminus, may be involved in phosphorylation-mediated receptor desensitization (Okwu et al., 1992). Indeed, desensitization of TP receptors has been reported (Murray and FitzGerald, 1989). The carboxy terminal cytoplasmic tail is also short, and there is no cysteine residue in this region, suggesting that the C termini of these receptors are not membrane tethered by myristoylation but present free in the cytoplasm.

There has been some controversy regarding the existence of TP receptor subtypes (Halushka et al., 1989; Ogletree and Allen, 1992). To clarify this issue, Nüsing et al. (1993) cloned and characterized the gene for the TP receptor from a human genomic library. The gene is present as a single copy per haploid, spans 15 kb and contains three exons divided by two introns. The first intron is 6.3 kb long and exists in the 5′-noncoding region, 83 bp upstream from the ATG start site. Intron 2 is 4.3 kb long and is located at the end of the sixth putative transmembrane domain and separates it from the downstream coding region. When reverse transcription and polymerase chain reaction analysis using primers flanking intron 2 was performed on poly(A)$^+$ RNA from MEG-01 cells, human placenta, and mesangial cells, it amplified only a single DNA fragment having the expected size of 173 bp. This suggests that no alternative splicing of the coding region occurs and that only one type of TP receptor protein is formed from this gene in these cells. Although these findings cannot exclude the presence of a less homologous TP receptor, they provide support for the existence of a single form of the TP receptor in both platelets and smooth muscle cells. The chromosomal localization of this receptor gene was assigned to 19p13.3 of the human chromosome. The mouse TP receptor gene (*Txa2r*) has been mapped to chromosome 10 (Taketo et al., 1994).

III. Conclusions

The classification of prostanoid receptors was originally based solely on functional data, obtained by means of comparisons of rank orders of agonist activity, and where possible, also the effects of antagonists. A comprehensive classification was developed using this approach, which covered many, if not all, of the actions of prostanoids. Broadly speaking, the classification has also proved consistent with the developing knowledge of second-messenger coupling. Thus, DP, EP_2, and IP receptors are coupled at least predominantly to G_s, EP_3 to G_i and G_q, and FP and TP largely to G_q. The emerging molecular biology of the prostanoid receptors fully supports the functional classification, with EP_1, EP_2 (or EP_4), EP_3, FP, IP, and TP receptor cDNAs so far having been cloned. So far, no orphan prostanoid receptor cDNA has been cloned. Our understanding of EP_3 receptors has been considerably expanded by the knowledge that splice variants exist, and these exhibit quite distinct characteristics with respect to second-messenger coupling. Doubtlessly, the DP receptor will soon be cloned, and we will gain insight into whether there also exist subtypes of DP, FP, IP, and TP receptors. It is an exciting time for prostanoid research, but it is a sobering thought that when the vast numbers of prostanoid analogues were being synthesised in the 1970s and 1980s, little was known about the receptors at which prostanoids act. Without the benefits of our current level of understanding, it seems that much of this chemical effort was premature. Many of these compounds should now be reevaluated. During the next decade, we will learn a lot more about prostanoid receptors, their species variance, their structural diversity, their function, their distribution, and the potential for their therapeutic exploitation with agonists and antagonists.

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