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Selective prostaglandin D_2 receptor stimulation elicits ocular hypotensive effects in rabbits and cats

Takeshi Matsugi [a,*], Masaaki Kageyama [a], Kazuo Nishimura [a], Heather Giles [b], Eiichi Shirasawa [a]

[a] *Developmental Research Laboratories, Santen Pharmaceutical Co., Ltd., 3-9-19 Shimoshinjo, Higashiyodogawa-ku, Osaka 533, Japan*
[b] *Biochemical Sciences, The Wellcome Research Laboratories, Langley Court, South Eden Park Road, Beckenham, Kent BR3 3BS, UK*

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Abstract

The effects of the selective prostaglandin D_2 (DP) receptor agonists, 572C85 ((±)-5-(3-carboxypropylthio)-1-(2-cyclohexyl-2-hydroxyethyl-amino)hexahydrocyclopenta(*d*)imidazol-2(1*H*)-one) and 192C86 ((±)-5-(3-carboxypropylthio)-1-(2-cyclohexyl-2-hydroxyethylidene-amino)-3-ethylhexahydrocyclopenta(*d*)imidazol-2(1*H*)-one), were determined on intraocular pressure regulation in rabbits and cats. 572C85 (50 μg) in rabbits maximally lowered intraocular pressure by 4.3 mm Hg, and significantly for 4 h compared to control. In cats 572C85 had a similar effect. 192C86 (50 μg) reduced intraocular pressure by 2.8 mm Hg for 2 h in rabbits. Following exposure to the specific DP receptor antagonist, BW A868C ((±)-3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino)-hydantoin; 50 μg), which had no effect on intraocular pressure by itself, 572C85 (50 μg) did not reduce intraocular pressure in rabbits and cats. The intraocular pressure lowering effect of the mixed DP and EP receptor agonist, BW245C (5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)-hydantoin; 50 μg), in cats was suppressed by only 64% by BW A868C (50 μg). These results clearly show that the DP receptors in rabbit and cat eyes are involved in intraocular pressure regulation. However, under baseline conditions DP receptor activity does not contribute to this regulation.

Keywords: DP receptor; 572C85; BW A868C; Intraocular pressure; (Rabbit); (Cat)

1. Introduction

Prostaglandin D_2 receptor activity has been implicated in the regulation of vasodilatation (Wasserman et al., 1977; Narumiya and Toda, 1985), bronchoconstriction (Wasserman et al., 1977) and inhibition of platelet aggregation (Whittle et al., 1978). This receptor subtype is designated as DP (Kennedy et al., 1982; Coleman et al., 1984) and it has been reported to be involved in intraocular pressure regulation in rabbits (Goh et al., 1988a,b; Woodward et al., 1990), cats (Woodward et al., 1991) and humans (Nakajima et al., 1991), because the DP receptor agonist, prostaglandin D_2, and its stable analogue, BW245C, produce ocular hypotensive effects in these species. However, the sole involvement of DP receptors in these responses could not be defined. Prostaglandin D_2 also has efficacy at many other prostanoid receptors (Giles et al., 1991), particularly at FP (Coleman et al., 1984) and TP receptors (Hamid-Bloomfield et al., 1990). BW245C also has an affinity and efficacy for at least one of the EP class of receptors (Giles et al., 1989). Therefore, the role of DP receptors in intraocular pressure regulation requires additional clarification.

In the present study, we used two highly selective DP receptor agonists, 572C85 and 192C86 (Leff and Giles, 1992), to identify more precisely the role of DP receptor activity in the regulation of intraocular pressure in rabbits and cats. Our use of these agonists in combination with the specific DP receptor antagonist, BW A868C (Hamid-Bloomfield and Whittle, 1989; Giles et al., 1989; Trist et al., 1989), clearly establishes that the selective stimulation of DP receptors has significant intraocular pressure lowering effects in rabbits and cats.

* Corresponding author. Tel. 06-321-7038, fax 06-321-2955.

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2. Materials and methods

2.1. Experimental procedure

All experiments were conducted in accordance with the Declaration of Helsinki. Male Japanese White rabbits weighing 2.5–3.5 kg and male European cats weighing 4.0–5.0 kg were housed on a 12 h light-dark cycle (lights on at 07:00 h), with room temperature maintained at 23 ± 1°C and humidity at 55 ± 10%, and food and water available ad libitum. In all experiments, the animals were unrestrained and were not systemically treated with any drugs, such as systemic anesthetics and muscle relaxants. Each animal was pretrained to accept measurements of intraocular pressure with a calibrated pneumatic tonometer (Alcon). Intraocular pressure was measured after corneal anesthesia with topical application of 0.4% (for rabbits) or 0.1% (for cats) oxybuprocaine hydrochloride solution. The local anesthetic had no effect on intraocular pressure. Before each intraocular pressure measurement, the anterior segment of each eye was macroscopically observed for irritation. All drug solutions were prepared just before each experiment, and 50 μl of a drug was topically applied. In rabbits, drug solutions or vehicle were unilaterally applied, and the contralateral eye remained untreated, allowing use of the eye as the control. In cats, the solutions were applied bilaterally. BW A868C was topically applied 30 min before the instillation of a DP receptor agonist. Each animal received at least two doses in a random fashion, but did not receive the same dose of one drug. The interval between two experiments was at least 1 week.

2.2. Drugs

(±)-5-(3-Carboxypropylthio)-1-(2-cyclohexyl-2-hydroxyethyl-amino)hexahydrocyclopenta(*d*)imidazol-2(1*H*)-one (572C85), (±)-5-(3-carboxypropylthio)-1-(2-cyclohexyl-2-hydroxyethylidene-amino)-3-ethylhexahydrocyclopenta(*d*)imidazol-2(1*H*)-one (192C86), 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)hydantoin (BW245C), and (±)-3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino)-hydantoin (BW A868C) were supplied by Wellcome Research Laboratories, Beckenham, Kent, UK. The drugs were dissolved in a vehicle containing glycerin and polysorbate 80. These solutions were then diluted with the vehicle to the desired concentration.

2.3. Analysis of data

All data are expressed as the mean ± S.E.M. Statistical significance was determined by Student's *t*-test, Dunnett's multiple comparison test or Duncan's multiple comparison test.

3. Results

3.1. Effects of 572C85, 192C86 and BW245C on intraocular pressure in rabbits

In Fig. 1, the changes in intraocular pressure caused by these DP receptor agonists are expressed as differences between the treated and the untreated eyes. 572C85 (panel a) at 10 and 50 μg significantly reduced the intraocular pressure for 1 and 4 h, respectively. The maximal intraocular pressure reductions with these doses were 2.4 ± 0.5 and 4.3 ± 0.5 mm Hg, which occurred at 0.5 or 1 h, respectively. However, 50 μg of 192C86 (panel b) could significantly reduce intraocular pressure only by 2.8 ± 0.6 mm Hg at 0.5 h for 2 h. No initial increase in the intraocular pressure was observed with 572C85 or 192C86. A less selective DP receptor agonist, BW245C (panel c), at 50 μg also significantly reduced intraocular pressure by 2.4 ± 0.9 mm Hg for 4 h. Neither 572C85, 192C86 nor BW245C

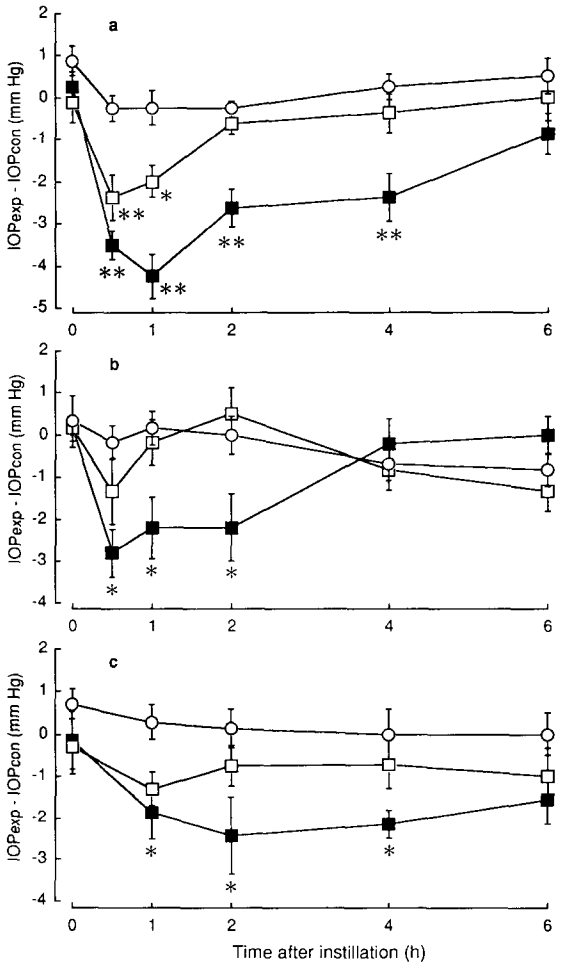

Fig. 1. Effects of (a) 572C85, (b) 192C86 and (c) BW245C on intraocular pressure (IOP) in rabbits. IOP responses to vehicle (○), 10 μg (□) and 50 μg (■) of drug. Each value represents the mean ± S.E.M. for 5–8 eyes. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. vehicle (by Dunnett's multiple comparison test).

affected the intraocular pressure in the contralateral eye, suggesting that they locally act in the eyes. No change in pupillary diameter and no conjunctival hyperemia were observed after instillation of each agonist.

3.2. Effect of BW A868C on intraocular pressure responses to 572C85 in rabbits

Fig. 2 shows the dose-dependent effects of pre-exposure to the specific DP receptor antagonist, BW A868C, on the hypotensive responses to 572C85 (50 μg). BW A868C (50 μg) by itself had no effect on intraocular pressure (panel a), but both 10 and 50 μg of BW A868C completely eliminated the hypotensive effects of 572C85 (50 μg) (panel b).

3.3. Effects of 572C85, 192C86 and BW245C on intraocular pressure in cats

In Fig. 3, the changes in intraocular pressure in cats caused by these DP receptor agonists are expressed as differences from their pre-dosing value. Both 572C85 (panel a) and 192C86 (panel b) at doses of 10–250 μg significantly reduced intraocular pressure. Their hypotensive effects were dose dependent, and their maximal effects occurred at 50 μg, and at same time point. The intraocular pressure decreases were between 2 and 5.5 mm Hg, and lasted for up to 4 h at doses above 50 μg. BW245C (panel c) at doses of 10 and 250 μg produced significant decreases in intraocular pressure of 3.4 ± 1.1 and 6.5 ± 1.3 mm Hg, respectively, which at 250 μg lasted for 2 h. Neither 572C85, 192C86 nor BW245C affected the pupillary diameter of each cat. 572C85 and 192C86 at 250 μg, and BW245C at more than 50 μg caused conjunctival hyperemia which lasted for 1–4 h.

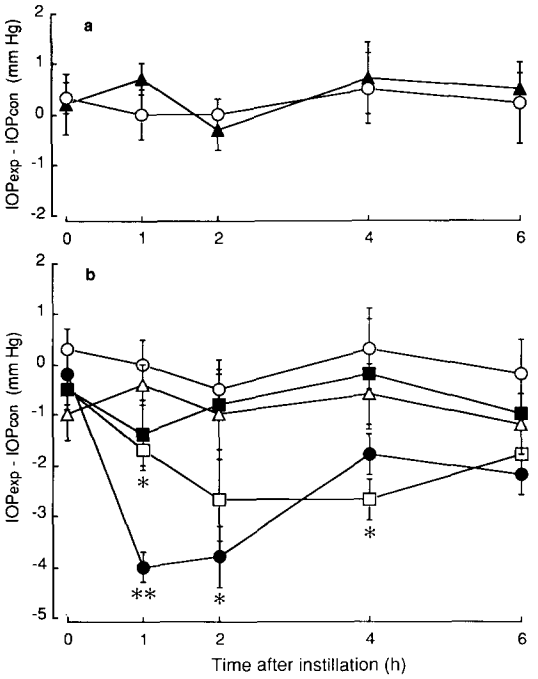

Fig. 2. (a) Time course of changes in intraocular pressure (IOP) in rabbits in the absence (○) and presence of 50 μg of BW A868C (▲). BW A868C or its vehicle was applied at 0 time. Each value represents the mean ± S.E.M. for 6 eyes. There was no significant difference between the IOPs in the absence and presence of BW A868C (by Student's unpaired *t*-test). (b) Antagonistic effects of BW A868C on the ocular hypotensive responses to 50 μg of 572C85 at the following concentrations (number of eyes in parentheses): zero (●) (5); 2 μg (□) (6); 10 μg (■) (5); 50 μg (△) (5). Vehicle treatment is represented with (○) (6). Each value represents the mean ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. vehicle (by Dunnett's multiple comparison test).

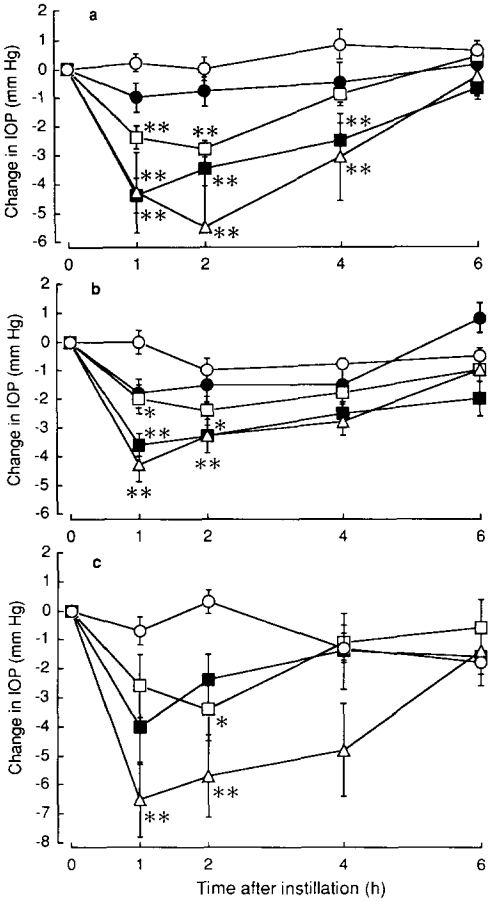

Fig. 3. Effects of (a) 572C85, (b) 192C86 and (c) BW245C on intraocular pressure (IOP) in cats. IOP responses to vehicle (○), 2 μg (●), 10 μg (□), 50 μg (■) and 250 μg (△) of drugs. Each value represents the mean ± S.E.M. for 4–16 eyes. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. vehicle (by Dunnett's multiple comparison test).

3.4. Effects of BW A868C on intraocular pressure responses to 572C85 and BW245C in cats

Fig. 4 shows the effect of pre-exposure to 50 μg of BW A868C on the ocular hypotensive effects of 572C85

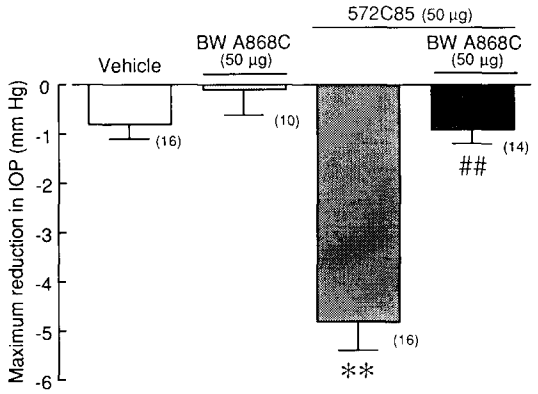

Fig. 4. Antagonist effects of BW A868C on the ocular hypotensive responses to 50 μg of 572C85 in cats. Each value represents the mean ± S.E.M. The number of eyes is shown in parentheses. The peak reductions in intraocular pressure (IOP) occurred at 2.0 ± 0.3 h (vehicle), 1.6 ± 0.3 h (BW A868C), 1.3 ± 0.1 h (572C85), 1.8 ± 0.3 h (combined BW A868C and 572C85), respectively. $^{**}P < 0.01$ vs. vehicle, $^{\#\#}P < 0.01$ vs. 572C85 alone (by Duncan's multiple comparison test).

(50 μg). This concentration of BW A868C was chosen because it was the highest one which we used in rabbits. 572C85 (50 μg) by itself significantly reduced the intraocular pressure by 4.8 ± 0.6 mm Hg at 1.3 ± 0.1 h. However, after exposure to 50 μg of BW A868C for 30 min, 572C85 had no hypotensive effect. As in rabbits, BW A868C by itself had no effect on the intraocular pressure. In Fig. 5, the effects are shown of pre-exposure to 50 μg of BW A868C on the ocular hypotensive effects of BW245C (50 μg). BW245C elicited a mean reduction in intraocular pressure of 5.8 ± 0.6 mm Hg after 2.4 ± 0.4 h. Following exposure

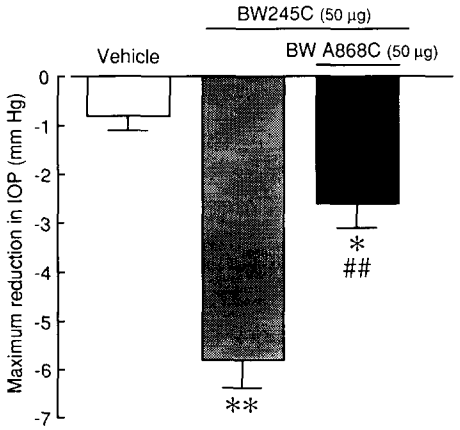

Fig. 5. Antagonist effects of BW A868C on the ocular hypotensive responses to 50 μg of BW245C in cats. Each value represents the mean ± S.E.M. for 12 eyes. The peak reductions in intraocular pressure (IOP) occurred at 2.0 ± 0.3 h (vehicle), 2.4 ± 0.4 h (BW245C), 1.8 ± 0.6 h (combined BW A868C and BW245C), respectively. $^{**}P < 0.01$, $^{*}P < 0.05$ vs. vehicle, $^{\#\#}P < 0.01$ vs. BW245C alone (by Duncan's multiple comparison test).

to 50 μg of BW A868C for 30 min, the intraocular pressure reduction induced by BW245C was only partially suppressed by 64%. Thus, BW245C significantly reduced intraocular pressure even after exposure to BW A868C, a specific DP receptor antagonist.

4. Discussion

There is evidence for the involvement of DP receptors in the regulation of intraocular pressure in rabbits and cats based on the hypotensive effects of DP receptor agonists, prostaglandin D_2 (Goh et al., 1988a,b) and its stable analogue, BW245C (Goh et al., 1988b; Woodward et al., 1990, 1991, 1993), and SQ 27986 (Woodward et al., 1993). However, in rabbits, prior exposure to the selective DP receptor antagonist, BW A868C (25 μg), did not fully eliminate the hypotensive response to BW245C (Woodward et al., 1993), even though BW A868C is the most selective DP receptor antagonist currently available (Hamid-Bloomfield et al., 1990; Giles et al., 1989; Trist et al., 1989). This partial suppression could mean that BW245C is not completely selective for DP receptors. Furthermore, consistent with this notion, BW245C also binds to an atypical EP_2 receptor in rabbit jugular vein (Giles et al., 1989). With regard to prostaglandin D_2, this agonist also binds to other prostaglandin receptors (Giles et al., 1991), particularly to FP and TP receptors in vascular and airway smooth muscles (Coleman et al., 1984; Hamid-Bloomfield et al., 1990). In the case of SQ 27986, its selectivity was not validated in rabbits by determining if any DP receptor antagonist could suppress its ocular hypotensive effect (Woodward et al., 1993). Therefore, the involvement of DP receptors in intraocular pressure regulation required further clarification.

We were able to re-examine this question in rabbits and in cats with two highly specific DP receptor agonists, 572C85 and 192C86, previously used in rabbit jugular vein and platelets (Leff and Giles, 1992). We found that these agonists significantly lowered intraocular pressure in rabbits and cats, but that 572C85 elicited a slightly larger maximum effect than 192C86, consistent with the lower efficacy of 192C86 demonstrated in rabbit jugular vein and human platelets (Giles et al., 1991). Furthermore, in rabbits the specific DP receptor antagonist, BW A868C, dose and time dependently inhibited the hypotensive effects of 572C85. In cats, BW A868C also eliminated the effect of 572C85. It had been unclear from previous studies whether or not a DP receptor antagonist could suppress a hypotensive response to a DP receptor agonist in cats (Woodward et al., 1991). These results clearly suggest that DP receptors are involved in intraocular pressure regulation in cats as well as rabbits.

We found that a specific DP receptor antagonist, BW A868C, by itself had no effect on intraocular pressure in rabbits and cats. This observation has two possible explanations: (1) there is no coupling of DP receptors to cell signaling pathways which are involved in intraocular pressure regulation; (2) the endogenous levels of prostaglandin D_2 are too low to stimulate DP receptor activity. Earlier (Woodward et al., 1993) and our studies demonstrated that topically applied DP receptor agonists produced ocular hypotensive effects, which were eliminated by BW A868C in rabbits and cats. Unilateral instillation of DP receptor agonists in rabbits did not affect the intraocular pressure in the contralateral eye, suggesting that these agonists act locally on intraocular pressure effectors in the eyes. Furthermore, in the isolated rabbit iris-ciliary body, DP receptor agonists stimulated adenylate cyclase (Bhattacherjee et al., 1993) and in isolated cat ciliary muscles they elicited relaxation (Chen and Woodward, 1992), and these effects were inhibited by BW A868C. Thus, the first explanation can be eliminated. It has been demonstrated that basal levels of prostaglandins are extremely low in aqueous humor of normal rabbits (Eakins et al., 1972; Weinreb et al., 1985). In addition, a cyclooxygenase inhibitor, indomethacin, did not affect intraocular pressure, when topically applied to rabbit eyes (Anderson and Wilson, 1990). Therefore, under basal conditions, prostaglandin receptor activities including DP may not be sufficiently stimulated to modulate intraocular pressure.

The prostaglandin D_2 analogue, BW245C, was previously used in rabbits to determine a role for DP receptor activity in intraocular pressure regulation (Goh et al., 1988b; Woodward et al., 1990). In rabbits, DP receptor involvement was identified because BW245C (25 μg) had a marked significant hypotensive effect that lasted for 3 h and in the latter study all of the responses occurring after 2–3 h were eliminated by pre-exposure to 25 μg of BW A868C (Woodward et al., 1990,1993). Unexplainedly, at 1 and 4 h, a significant decrease in intraocular pressure occurred in the combined presence of BW245C and BW A868C (Woodward et al., 1993). These decreases were probably not caused by BW A868C because it had no significant hypotensive effect by itself in our study. However, we found that only 10 μg of BW A868C was needed to eliminate the maximum hypotensive effect of 572C85 (50 μg). In contrast, the response to a sub-maximal concentration of BW245C (50 μg) was only partially inhibited by 50 μg of BW A868C, providing strong evidence that BW245C was activating two receptors, one of which was resistant to antagonism by BW A868C. Since BW245C is known to activate a DP receptor and an atypical EP_2 receptor in rabbit jugular vein (Giles et al., 1989), it could be that both the DP and EP_2 receptors are involved in the response to BW245C.

There was a species difference between the inhibitory effect of BW A868C on the intraocular pressure response to BW245C: BW A868C was more effective in rabbits than in cats. Stimulation of EP_2 receptors has been shown to reduce intraocular pressure in cats, but not in rabbits (Waterbury et al., 1990; Woodward et al., 1991). This means that there are no EP_2 receptors which are involved in the regulation of intraocular pressure in rabbits. Because our study suggests that BW245C reduces intraocular pressure by stimulating DP and EP_2 receptors, the species difference between rabbits and cats can be explained by the lack of EP_2 receptors in rabbits.

In conclusion, we found that the highly selective DP receptor agonists, 572C85 and 192C86, significantly lowered the intraocular pressure in rabbits and cats. Furthermore, a specific DP receptor antagonist, BW A868C, completely eliminated the hypotensive effects of 572C85 in both species. The failure of BW A868C to affect baseline intraocular pressure could mean that endogenous levels of prostaglandin D_2 are lower than those needed for DP receptors to modulate intraocular pressure in rabbits and cats. 572C85 is a useful agonist for describing a role for DP receptors in intraocular pressure regulation.

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