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Identification of the dopamine autoreceptor in the guinea-pig retina as D_2 receptor using novel subtype-selective antagonists

[1]Bernd Weber, *,[1]Eberhard Schlicker, [2]Pierre Sokoloff & [3]Holger Stark

[1]Institut für Pharmakologie und Toxikologie, Universität Bonn, Reuterstr. 2b, 53113 Bonn, Germany; [2]Unité de Neurobiologie et de Pharmacologie Moléculaire, Centre Paul Broca de l'INSERM (U. 109), 2 ter rue d'Alésia, 75014 Paris, France and [3]Institut für Pharmazeutische Chemie, Biozentrum, Johann Wolfgang Goethe-Universität Frankfurt am Main, Marie-Curie-Str. 9, 60439 Frankfurt am Main, Germany

1 Dopamine release in the retina is subject to modulation *via* autoreceptors, which belong to the D_2 receptor family (encompassing the D_2, D_3 and D_4 receptors). The aim of the present study was to determine the receptor *sub*type (D_2 vs D_3) involved in the inhibition of dopamine release in guinea-pig retinal discs, using established (haloperidol, (*S*)-nafadotride) and novel dopamine receptor antagonists (ST-148, ST-198).

2 hD_{2L} and hD_3 receptors were expressed in CHO cells and the pK_i values determined in binding studies with [^{125}I]-iodosulpride were: haloperidol 9.22 vs 8.54; ST-148 7.85 vs 6.60; (*S*)-nafadotride 8.52 vs 9.51; ST-198 6.14 vs 7.92.

3 The electrically evoked tritium overflow from retinal discs preincubated with [^{3}H]-noradrenaline (which represents quasi-physiological *dopamine* release) was inhibited by the dopamine receptor agonists B-HT 920 (talipexole) and quinpirole (maximally by 82 and 71%; pEC_{50} 5.80 and 5.83). The concentration-response curves of these agonists were shifted to the right by haloperidol (apparent pA_2 8.69 and 8.23) and ST-148 (7.52 and 7.66). (*S*)-Nafadotride 0.01 μM and ST-198 0.32 μM did not affect the concentration-response curve of B-HT 920.

4 The dopamine autoreceptor in the guinea-pig retina can be classified as a D_2 receptor. ST-148 and ST-198 show an improved selectivity for D_2 and D_3 receptors when compared to haloperidol and (*S*)-nafadotride, respectively.

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Abbreviations: B-HT 920, 6-allyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepin-2-amine; CHO, Chinese hamster ovary; PSS, physiological salt solution; S, electrical stimulation; ST-148, *N*-(4-[4-(2-methoxyphenyl)-piperazin-1-yl]-butyl)-5-(dimethylamino)-naphthalene-1-sulphonamide; ST-198, *N*-(4-[1,2,3,4-tetrahydroisoquinolin-2-yl]-butyl)-3-phenylacrylamide; t, collection period in which basal tritium efflux was determined

Introduction

Dopamine is located in the amacrine and interplexiform cells of the inner nuclear layer of the retina (Smeets & Gonzalez, 2000). In the guinea-pig retina dopamine has recently been shown to be localized to amacrine cells type 1 and 2 (Oh *et al*., 1999). Some inherent functions of the retina involve the release of dopamine, e.g., dark-light adaptation (Djamgoz & Wagner, 1992) or motion detection (Mora-Ferrer & Gangluff, 2000).

Retinal dopamine release is subject to modulation *via* inhibitory autoreceptors, which have been identified in the retina of teleosts (Rashid *et al*., 1993), rabbits (Dubocovich & Weiner, 1985) and guinea-pigs (Weber *et al*., 2001), and belong to the dopamine D_2-subfamily (which encompasses the D_2, D_3 and D_4 receptors; for review, see Strange, 2001). For some dopamine autoreceptors located outside the retina, e.g., in the brain, the dopamine receptor subtype within the dopamine D_2-subfamily has been determined. The autoreceptor in the human neocortex and in the rat striatum can be subclassified as D_2 (Fedele *et al*., 1999) whereas the autoreceptor on the tuberoinfundibular neurones of the rat is D_3 (Lin *et al*., 2000). It may be of particular interest to determine the exact receptor subtype also for the dopamine autoreceptor in the retina since dopamine in the retina is highly relevant with respect to experimental models of myopia (e.g., deprivation myopia in chickens is aggravated by the D_2/D_3 receptor antagonist sulpiride; Schaeffel *et al*., 1995).

In a study on guinea-pig retinal discs carried out for this purpose, we used haloperidol and (*S*)-nafadotride, which have a preference for the D_2- or D_3-receptor subtypes, respectively, and two novel substances ST-148 and ST-198, with a higher degree of selectivity for the D_2- and D_3-receptor subtypes, respectively (for chemical structures, see Figure 1). The agonists used in the present study, quinpirole and B-HT 920, possess a preference for the D_3 over the D_2 receptor (Levant, 1997; Wood *et al*., 2000). All experiments were performed on retinal discs preincubated with [^{3}H]-noradrenaline, which in areas devoid of noradrenergic neurones like the retina of the guinea-pig is taken up (and released from) dopaminergic cells and offers advantages over the use of [^{3}H]-dopamine itself (Schlicker *et al*., 1996).

*Author for correspondence; E-mail: e.schlicker@uni-bonn.de

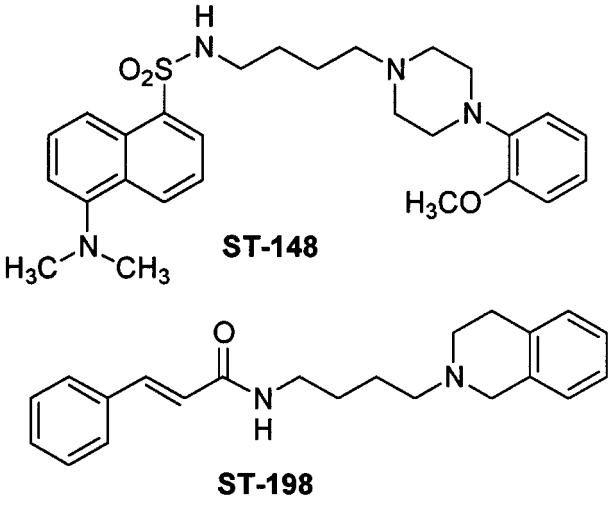

Figure 1 Chemical structures of the novel dopamine D_2 (ST-148) and D_3 (ST-198) receptor antagonists.

Methods

Superfusion experiments

Male Dunkin-Hartley guinea-pigs were decapitated and the eyes were removed from the skull. The retina was carefully detached from other layers of the eye using a spatula and discs (diameter 3 mm) were punched out. For the experiments, a physiological salt solution (PSS) of the following composition was used (mM): NaCl 118, KCl 4.8, $CaCl_2$ 1.3, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, ascorbic acid 0.06, disodium EDTA 0.03, glucose 10; the solution was aerated with 95% O_2 and 5% CO_2 (pH 7.4).

Retinal discs preincubated with [^{3}H]-noradrenaline 25 nM (specific activity 51.8–57.3 Ci mmol^{-1}) (60 min; 37°C) were superfused with PSS (37°C) for 110 min. Tritium overflow was evoked by two 2-min periods of stimulation (3 Hz, 200 mA, 2 ms) after 40 and 90 min (S_1, S_2). In all experiments the PSS contained nomifensine 10 μM throughout superfusion. The antagonists under study were present in the PSS throughout superfusion, whereas the agonists were added to the PSS from 62 min of superfusion onward.

Binding studies

Membranes of CHO cell lines stably transfected with human dopamine D_{2L} or D_3 receptor DNA were taken for binding assays using [^{125}I]-iodosulpride according to Sautel *et al.* (1995). Nonspecific binding was determined in the presence of emonapride 1 μM. K_i values were derived from IC_{50} values according to the Cheng-Prussoff equation (Cheng & Prussoff, 1973), taking into account the K_d of [^{125}I]-iodosulpride for the respective receptors. Data were obtained from at least three separate experiments.

Calculations and statistics

Tritium overflow was calculated as the fraction of the tritium content of the slices at the beginning of the respective collection period (fractional rate of tritium efflux). Basal tritium efflux was quantified by calculating the ratio of the fractional rate in the 5-min period immediately before S_2 (i.e. from 85–90 min; t_2) over that in the collection period from 55–60 min (t_1, i.e. in the 5-min sample collected just before the addition of the agonist to the superfusion medium). Stimulation-evoked tritium overflow was calculated by subtraction of the basal from the total tritium efflux during stimulation and the subsequent 13 min and was expressed as per cent of tritium present in the slice at the onset of stimulation (basal tritium efflux was assumed to decline linearly from the 5-min collection period before that to 15–20 min after onset of stimulation). To quantify the effects of agonists on the stimulated tritium overflow, the ratio of the overflow evoked by S_2 over that evoked by S_1 was determined. To determine the effects of antagonists on the evoked overflow, the S_1 values obtained in the presence and absence of the respective antagonist were compared. To quantify agonist potencies, pEC_{50} values (negative logarithms of the concentration causing the half-maximal effect) were determined. Apparent pA_2 values for antagonists were calculated according to formula 4 of Furchgott (1972).

Results are given as means ± s.e.mean of n experiments. For comparison of mean values, Student's t-test was used; the Bonferroni correction was used, when two or more values were compared to the same control.

Drugs

(−)-[Ring-2,5,6-^{3}H]noradrenaline (NEN, Zaventem, Belgium); [^{125}I]-iodosulpride (Amersham Int., Buckinghamshire, U.K.); tetrodotoxin (Roth, Karlsruhe, Germany); haloperidol, quinpirole hydrochloride (RBI/Sigma, Munich, Germany); B-HT 920 (talipexole; 6-allyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepin-2-amine dihydrochloride; Thomae, Biberach an der Riss, Germany); nomifensine (Hoechst, Frankfurt); emonapride (Yamanouchi, Tokyo, Japan); ST-148 (*N*-(4-[4-(2-methoxyphenyl)-piperazin-1-yl]-butyl)-5-(dimethylamino)-naphthalene-1-sulphonamide) maleate and ST-198 (*N*-(4-[1,2,3,4-tetrahydroisoquinolin-2-yl]-butyl)-3-phenylacrylamide) maleate were synthesized by H. Stark; (*S*)-nafadotride (synthesized at the Unité de Neurobiologie et Pharmacologie Moléculaire, Centre Paul Broca). Stock solutions of the drugs were prepared with water, citrate buffer (0.1 mM, pH 4.8; tetrodotoxin), lactic acid (2 M; emonapride), HCl 0.01 M (haloperidol) or DMSO (ST-148, ST-198) and diluted to the concentration required. The solvents did not affect basal and evoked tritium overflow by themselves.

Results

Superfusion experiments

Basal tritium efflux was expressed as t_1 or t_2/t_1. The t_1 value was not affected by any of the antagonists under study (Table 1). The t_2/t_1 value was 0.58 ± 0.08 in 43 control experiments in which no agonist or antagonist was present; similar t_2/t_1 values were obtained in experiments in which no agonist but one of the four antagonists was present (results not shown). B-HT 920 0.1–320 μM, quinpirole 0.1–100 μM, tetrodotoxin 1 μM and omission of Ca^{2+} ions did not alter t_2/t_1 values (results not shown).

The electrically evoked tritium overflow was expressed as S_1 or S_2/S_1. To quantify the effects of antagonists (present in the medium during S_1 and S_2), S_1 values were used. To quantify the effects of agonists (present in the medium during S_2), S_2/S_1 values were considered. S_1 values are shown in Table 1. S_2/S_1 values in agonist-free controls are given in the legends to Figures 2 and 3.

The electrically evoked tritium overflow (S_2/S_1) was inhibited by $96\pm1\%$ and $99\pm1\%$ by tetrodotoxin 1 μM or omission of Ca^{2+} ions, respectively ($n=5-8$). The dopamine receptor agonists B-HT 920 and quinpirole inhibited the S_2/S_1 value in a concentration-dependent manner (Figures 2 and 3). The effect of either agonist became significant from 1 μM onward and the maximum effect was obtained at 100 μM; the extent of inhibition obtained for B-HT 920 100 μM ($82\pm1\%$; $n=14$) was significantly ($P<0.005$) higher than that obtained for quinpirole 100 μM ($71\pm2\%$; $n=14$). The negative logarithm of the concentration causing the half-maximum inhibitory effect (pEC_{50}) was 5.80 and 5.83 for B-HT 920 and quinpirole, respectively.

The concentration-response curve of B-HT 920 was shifted to the right by haloperidol 0.01 μM but not affected by the same concentration of (*S*)-nafadotride (Figure 2A). The novel antagonist ST-148 0.32 μM caused a dextral shift of the concentration-response curve of B-HT 920 whereas the same concentration of ST-198 failed to do so (Figure 2B). Haloperidol 0.01 μM and ST-148 0.32 μM also shifted to the right the concentration-response curve of the other dopamine agonist, quinpirole (Figure 3). The apparent pA_2 values obtained for the dopamine receptor antagonists are listed in Table 2. Compound ST-148 0.32 μM by itself facilitated the evoked overflow (S_1) by 15%, whereas the other antagonists had no significant effect (Table 1).

Binding studies

Binding of [^{125}I]-iodosulpride to hD_{2L} and hD_3 receptors expressed in CHO cells has been thoroughly characterized in the studies by Sokoloff *et al*. (1992) and Sautel *et al*. (1995) and the K_i values for haloperidol and (*S*)-nafadotride (Table

Table 1 Influence of the antagonists on basal and electrically evoked tritium outflow in guinea-pig retinal discs preincubated with [^{3}H]-noradrenaline

	Basal tritium efflux during t_1 (fractional rate; min^{-1})	*Tritium overflow evoked by S_1* (% of tissue tritium)
Control	0.0090 ± 0.0012	17.75 ± 0.60
Haloperidol 0.01 μM	0.0094 ± 0.0012	19.75 ± 1.33
(*S*)-Nafadotride 0.01 μM	0.0076 ± 0.0011	18.18 ± 1.47
ST-148 0.32 μM	0.0095 ± 0.0015	20.48 ± 0.96*
ST-198 0.32 μM	0.0096 ± 0.0022	19.80 ± 2.64

Tritium overflow was evoked after 40 min (S_1). Basal tritium efflux was determined in the 5-min sample from 55–60 min (t_1). Means$\pm$s.e.mean of 5-29 experiments. *$P<0.05$.

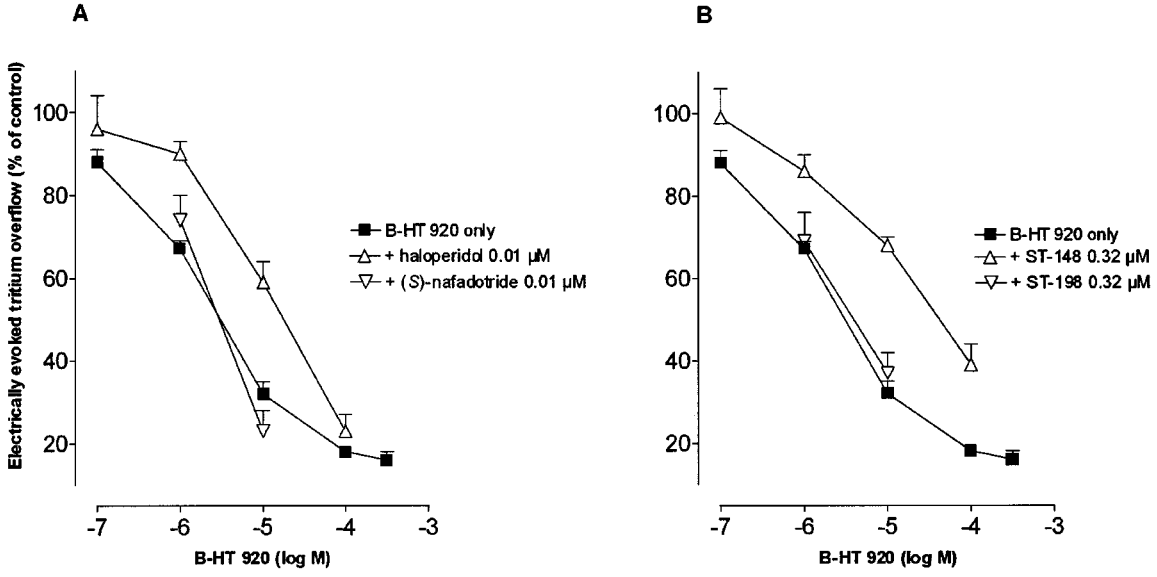

Figure 2 Effect of B-HT 920 on the electrically evoked tritium overflow from [^{3}H]-noradrenaline-preincubated retinal discs and interaction with dopamine receptor antagonists. (A) shows the two classical dopamine receptor antagonists, in (B) the novel antagonists are depicted. The antagonists were present throughout the superfusion (110 min), B-HT 920 from 62 min onward. Tritium overflow was stimulated after 40 and 90 min (S_1, S_2) and the ratio of the overflow evoked by S_2 over that evoked by S_1 was determined; results are given as per cent of the S_2/S_1 values in B-HT 920-free controls. The S_2/S_1 values in the five B-HT 920-free control series were: 0.86 ± 0.02 (no antagonist); 0.70 ± 0.02 (haloperidol); 0.93 ± 0.07 ((*S*)-nafadotride); 0.77 ± 0.03 (ST-148); 0.78 ± 0.03 (ST-198). Means$\pm$s.e.mean of 5–31 (B-HT 920 alone) and 4–7 independent superfusion experiments (in the presence of antagonists).

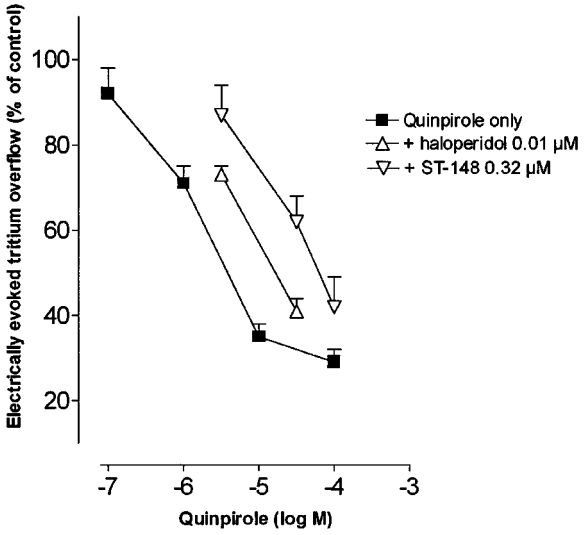

Figure 3 Effect of quinpirole on the electrically evoked tritium overflow from [^{3}H]-noradrenaline-preincubated retinal discs and interaction with dopamine D_2 receptor-selective antagonists. The antagonists were present throughout the superfusion (110 min), quinpirole from 62 min onward. Tritium overflow was stimulated after 40 and 90 min (S_1, S_2) and the ratio of the overflow evoked by S_2 over that evoked by S_1 was determined; results are given as per cent of the S_2/S_1 values in quinpirole-free controls. The S_2/S_1 values in the three quinpirole-free control series were: 0.86 ± 0.02 (no antagonist); 0.73 ± 0.02 (haloperidol); 0.75 ± 0.07 (ST-148). Means $\pm$s.e.mean of 7–16 (quinpirole alone) and 4–8 independent superfusion experiments (in the presence of antagonists).

Table 2 Apparent pA_2 values of the antagonists under study at the dopamine autoreceptor in the guinea-pig retina and their pK_i values at recombinant hD_2- and hD_3-receptors

	pA_2 in guinea-pig retina	*pK_i*	
		hD_{2L}	*hD_3*
Haloperidol	8.46[a] (8.69; 8.23)	9.22[c]	8.54[c]
ST-148	7.59[a] (7.52; 7.66)	7.85	6.60
(*S*)-Nafadotride	<8[b]	8.52[d]	9.51[d]
ST-198	<6.5[b]	6.14	7.92

[a]Mean value of the pA_2 values given in parentheses, which were obtained against B-HT 920 (Figure 2) and quinpirole (Figure 3). [b]From Figure 2. [c]From Sokoloff *et al.* (1992). [d]From Sautel *et al.* (1995).

2) were taken from these studies. Table 2 also shows the K_i values for the novel dopamine receptor antagonists ST-148 and ST-198. Compared to haloperidol and (*S*)-nafadotride, ST-148 exhibits an improved selectivity for hD_{2L} receptors and ST-198 has a higher preference for hD_3 receptors, respectively.

Discussion

The aim of our study was to characterize the release-regulating dopamine autoreceptor in the guinea-pig retina. The guinea-pig retinal discs were preincubated with [^{3}H]-noradrenaline, which is accumulated in dopaminergic cells in this avascular retina (Chase, 1982; Schlicker *et al.*, 1996) (and not in postganglionic sympathetic neurones innervating the retinal vasculature, like in porcine retina; Schlicker *et al.*, 1990). The electrically evoked tritium overflow, which is Ca^{2+} dependent and tetrodotoxin-sensitive, therefore represents quasi-physiological dopamine release (Schlicker *et al.*, 1996). [^{3}H]-Noradrenaline was employed instead of [^{3}H]-dopamine itself because of the lower variability of the results (Schlicker *et al.*, 1996). In all of the experiments, nomifensine 10 μM was used to block the dopamine transporter. The amount of dopamine release (expressed as stimulation-evoked tritium overflow divided by the tissue tritium content $\times$ 100) was almost 20% and much higher than in our previous studies on guinea-pig retinal discs in which, however, a blocker of the dopamine transporter was omitted and/or a lower stimulation frequency and/or current strength were used (Schlicker *et al.*, 1996; Schlicker & Kathmann, 1998).

The antagonistic effects of haloperidol, (*S*)-nafadotride, ST-148, and ST-198 were studied against quinpirole and B-HT 920. The latter is also a potent α_2-adrenoceptor agonist but the possibility that this property contributes to its inhibitory effect on dopamine release could be excluded (effect of B-HT 920 not antagonized by the α-adrenoceptor antagonist phentolamine; unpublished results). Surprisingly, the maximum inhibitory effect of quinpirole was less marked than that of B-HT 920 (whereas the pEC_{50} values of both drugs were identical), suggesting that quinpirole acts as a partial agonist. This finding is reminiscent of the results obtained in the study by Wood *et al.* (2000) in which both agonists were examined at recombinant hD_2 and hD_3 receptors in microphysiometry studies.

To determine the dopamine receptor subtype involved in the inhibitory effect of B-HT 920 or quinpirole the apparent pA_2 values of the four antagonists were compared to their pK_i values at hD_{2L} and hD_3 receptors (binding studies with [^{125}I]-iodosulpride on CHO cells) (Table 2). The apparent pA_2 values underestimate the true antagonist affinity since the antagonist, under the experimental conditions of the present study, is competing not only with the exogenously added agonist (B-HT 920 or quinpirole) but also with endogenously released dopamine. This is e.g. shown by the fact that dopamine release was facilitated, probably by interruption of the tonical activation of the dopamine autoreceptor, by ST-148 (and by haloperidol 0.1 μM, i.e. a 10 fold higher concentration than that used in this study; unpublished results). Taking into account this phenomenon it may be appropriate to add 0.5 log units to the apparent pA_2 value to get a more authentic estimate of the true affinity of the antagonists.

A look at Table 2 shows that the apparent pA_2 ($+0.5$ log units) values of the antagonists with preference for D_2 receptors (haloperidol, ST-148) and their pK_i values at hD_2 receptors agree well, suggesting the involvement of D_2 receptors. In harmony with this view, the effect of B-HT 920 was not antagonized by the antagonists with preference for D_3 receptors at concentrations exceeding their K_i values at hD_3 receptors by a factor of about 30. For comparison of potencies and affinities one may use in addition the ratios of antagonists with differing selectivity profile (Trendelenburg *et al.*, 1995). This approach also offers the advantage that the underestimation of the true antagonist dissociation constant is cancelled out. In Table 3 the four possible ratios between

Table 3 Comparison of the ratios of the K_B values for the dopamine receptor antagonists obtained in release studies with the ratios of their K_i values obtained in binding sites.

	Autoreceptor	*hD2L*	*hD3*
(*S*)-Nafadotride/Haloperidol	>2.9	5.01	0.11
ST-198/Haloperidol	>91.2	1202	4.17
(*S*)-Nafadotride/ST-148	>0.39	0.21	0.001
ST-198/ST-148	>12.3	51.3	0.05

the antagonists with D_2- and D_3-receptor preference have been listed. Again the values suggest that the dopamine autoreceptor in the guinea-pig retina is a D_2 receptor.

One point of concern is that the functional dopamine autoreceptor has been examined in retinal discs from an experimental animal rather than from humans and that the gpD_2 receptor (which, to the best of our knowledge, has not yet been cloned) may differ in its pharmacological properties from the hD_2 receptor. In a recent study, Dubocovich *et al.* (1997) used a similar approach like in the present study, i.e. they compared the potencies of a series of compounds at the melatonin heteroreceptor causing inhibition of dopamine release in retinal discs from an experimental animal, the rabbit, with their affinities for recombinant human melatonin receptors. Since enough native human retinal tissue is hardly available one might try in the future to perform release experiments in post mortem human retinal tissue or in cultured human retinal cells.

In conclusion, (i) the release-regulating autoreceptor for dopamine in guinea-pig retinal discs belongs to the D_2-subtype of the D_2-subfamily of dopamine receptors; (ii) the newly synthesized antagonists ST-148 and ST-198 strongly differentiate between the hD_2- and hD_3-subtype of dopamine receptors, and (iii) quinpirole acts as a partial agonist at the guinea-pig dopamine D_2 receptor in the retina.

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