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Receptor regulatory properties evident in the molecular similarity of dopamine receptor ligands and purine nucleotides

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Abstract

Computational studies have revealed similarities in the relative configurations of purine nucleotides and ligands for histamine, acetylcholine and adrenergic receptors. In common with other G-protein-regulated receptors, dopamine receptors are associated with specific changes in nucleotide levels during signal transduction processes. The purpose of this study was to investigate molecular similarity in dopamine receptor ligands and purine nucleotides. Molecular superimposition and fitting data for D1-like receptor ligands identified a pharmacophore in the adenine and ribose rings of ATP. D2-like agonists and antagonists related to a pharmacophore in the guanine and ribose rings of GTP. The results are consistent with the hypothesis that the dopamine receptor family may have evolved from receptors for the ATP and GTP nucleotides.

Introduction

Two populations of dopamine receptors, identified by pharmacological and biochemical techniques, have been categorized by gene cloning into five distinct receptor subtypes (Missale et al 1998). Dopaminergic ligands discriminate easily between the original D1and D2 populations, but with less success for members of each sub-family: D1 and D5 (D1-like); D2, D3, D4 (D2-like). The high and widespread expression of D1- and D2-like receptor genes in brain tissue reflects the importance of dopamine in locomotion, incentive motivation and neuroendocrine secretion (Vallone et al 2000). Outside the central nervous system, dopamine influences systemic blood pressure by acting on vascular smooth muscle and renal tubular cell receptors (Murphy 2000). Dopamine also regulates gastrointestinal mobility and melatonin release in the mammalian retina (Missale et al 1998; Tosini & Dirden 2000).

Dopamine receptors couple to cellular effector systems through $G_s\alpha$, $G_0\alpha$, $G_i\alpha$ and $G_z\alpha$ members of the G protein superfamily (Sidhu & Niznik 2000). Receptors of the D1-like population are positive regulators of cyclic AMP (cAMP). D1 isoforms in various tissues couple to $G_s\alpha$, whereas activation of adenyl cyclase by the D5 receptor is constitutive (Sidhu & Niznik 2000). Effector functions of D1-like receptors include the activation of phospholipases, inhibition of Na^+/K^+ ATPase and Na^+/H^+ antiporter activity, Ca^{2+} mobilization, and modulation of K^+ efflux (Sidhu & Nisnik 2000; Vallone et al 2000). D2-like receptors inhibit adenyl cyclase by coupling to $G_i\alpha$ and $G_z\alpha$ proteins and variously modulate phosphoinositide hydrolysis, Q-type high-voltage-activated Ca^{2+} ion channels and inwardly rectifying K^+ currents (Sidhu & Nisnik 2000; Vallone et al 2000). D3 receptors are weakly

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Table 1 Conformational analysis and molecular superimposition data for fitting dopamine agonists to guanosine triphosphate.

Molecule	Superimposed atomic distance (Å)			Torsion angles (°)		Intramolecular distance (Å)			RMS value
	N2	O2	O3			N2–O2	N2–O3	O2–O3	
GTP				O9-C9-C1-C5	−47	5.8	5.1	2.6	
				O9-C8-C7-O6	−68				
				C8-C7-O6-P3	168				
				C7-O6-P3-O5	168				
				O6-P3-O5-P2	155				
				P3-O5-P2-O4	30				
				O5-P2-O4-P1	90				
				P2-O4-P1-O11	−51				
Dopamine	0.05	0.14	0.13	C6-C1-C7-C8	98	6.0	5.0	2.8	0.0010
		(C2)	(C5)	C1-C7-C8-N2	−49	(N2–C2)	(N2–C5)	(C2–C5)	
Apomorphine	0.13	0.11	0.13			5.7	4.9	2.8	0.0063
S-ADTN	0.10	0.11	0.12			5.7	5.0	2.8	0.0122
NO-500	0.08	0.09	0.11			5.8	5.0	2.8	0.0028
		(N1)	(S3)			(N2–N1)	(N2–S3)	(N1–S3)	
S-PTHB	0.11	0.18	0.24			5.7	5.4	2.6	0.0387
			(C3)				(N2–C3)	(N1–C3)	
LY-141865	0.04	0.24	0.20			5.6	5.1	2.2	0.0157
[2-(1*H*-indol-4-yl)-ethyl] -dipropylamine+1.9 kcal	0.11	0.13	0.05	C5-C6-C7-C8	−57	5.6	5.0	2.5	0.0007
				C6-C7-C8-N2	−50				
				C7-C8-N2-C9	−77				
				C8-N2-C9-C10	169				
				N2-C9-C10-C11	−54				
				C7-C8-N2-C12	161				
				C8-N2-C12-C13	−82				
				N2-C12-C13-C14	177				

Values are for minimum energy conformers, unless otherwise shown. Atoms used for fitting are shown in brackets when they differ from the preceding molecule.

coupled to all three subunits of $G_i\alpha$, whereas D4 sites are coupled to PTX-sensitive and $G_z\alpha$ proteins (Sidhu & Nisnik 2000).

The diversity of receptor mechanisms attributable to the range of receptor subtypes, receptor coupling to the large group of heterotrimeric complexes and the dimerization of G-protein-coupled receptors is becoming more apparent (Tallman 2000). By initiating subtype specific interaction, through molecular interaction, dimerization has the capacity to achieve significant changes in cell function. For example, selective A_1 adenosine agonists negatively affect the high affinity binding of D1 receptors (Franco et al 2000). The activation of A_{2A} receptors leads to a decrease in receptor affinity for dopamine agonists acting on D2 receptors. Computer modelling studies have previously identified relative molecular similarity in the ligands of several neurotransmitter receptor classes and the nucleotides involved in cell signal transduction processes, adenosine triphosphate (ATP) and guanosine triphosphate (GTP) (Williams et al 1998, 1999). The present study investigates relative molecular similarity in dopamine receptor ligands and the same low energy conformations of ATP and GTP.

Materials and Methods

The Nemesis program (Oxford Molecular version 2.1) was used to carry out charge calculation, conformational analysis and superimposition of molecular structures. Three dimensional structures of apomorphine, clozapine, dihydroxynomifensine, sulpiride, tetrahydrodihydroxy-phenylbezazepine and trifluoperazine were obtained from the Chemical Databank Service, Daresbury, UK (Neumeyer et al 1973; McDowell 1980;

Table 2 Conformational analysis and molecular superimposition data for fitting dopamine antagonists to guanosine triphosphate.

Molecule	Superimposed atomic distance (Å)			Torsion angles (°)		Intramolecular distance (Å)			RMS value
	N2	O2	O3			N2–O2	N2–O3	O2–O3	
GTP						5.8	5.1	2.6	
		(C2)	(C5)			(N2–C2)	(N2–C5)	(C2–C5)	
Haloperidol	0.02	0.10	0.10	C5-C6-C7-C8	3	5.9	5.0	2.8	0.0042
				C6-C7-C8-C9	86				
				C7-C8-C9-C10	74				
				C8-C9-C10-N2	−59				
				C9-C10-N2-C11	−60				
			(N3)	C12-C13-C14-C15	42		(N2–N3)	(C2–N3)	
Trifluoperazine									
(a)	0.24	0.19	0.13	C8-N1-C9-C10	−59	6.2	5.3	2.5	0.0216
		(N3)	(S3)	N1-C9-C10-C11	−76	(N2–N3)	(N2–S3)	(N3–S3)	
(b)	0.32	0.31	0.30	C9-C10-C11-N3	134	5.3	4.8	3.0	0.0408
		(N5)	(C3)	C10-C11-N3-C1	164	(N2–N5)	(N2–C3)	(N5–C3)	
Clozapine	0.07	0.17	0.11	N4-C1-N3-C7	−128	5.6	5.2	2.5	0.0101
		(O2)	(C3)			(N2–O2)	(N2–C3)	(O2–C3)	
S-Sulpiride	0.09	0.19	0.10	C14-O2-C4-C3	178	5.6	5.1	2.4	0.0011
				O2-C4-C3-C7	0				
				C4-C3-C7-N4	10				
				C3-C7-N4-C8	−172				
				C7-N4-C8-C9	118				
				N4-C8-C9-N2	76				
				C8-C9-N2-C10	–20				
		(S2)		C9-N2-C10-C11	−169	(N2–S2)		(S2–C3)	
GR218231	0.02	0.05	0.03	C15-C14-C13-N2	55	5.8	5.1	2.5	0.0017
+1.5 kcal				C14-C13-N2-C19	102				
				C13-N2-C19-C18	−62				
				C12-C11-C10-N2	175				
				C11-C10-N2-C19	−156				
				C9-C8-C7-S2	−75				
				C8-C7-S2-C4	−62				
				C7-S2-C4-C3	141				
		(C2)	(C5)	C2-C1-O1-C21	177	(N2–C2)	(N2–C5)	(C2–C5)	
Ester 33	0.08	0.11	0.09	C5-C6-C7-C8	−91	6.0	5.2	2.8	0.0005
				C6-C7-C8-C9	60				
				C11-N2-C12-C13	151				
				N2-C12-C13-O5	122				
				C12-C13-O5-C14	−160				
				C13-O5-C14-C15	62				
		(N8)	(C3)	C14-C15-O6-C16	179	(N2–N8)	(N2–C3)	(N8–C3)	
L-745870	0.14	0.20	0.07	C7-C8-C9-N2	112	5.5	5.0	2.4	0.0006
				C8-C9-N2-C11	−69				
		(C7)	(C3)	C12-N4-C13-C14	116	(N2–C7)	(N2–C3)	(C7–C3)	
Zotepine	0.05	0.14	0.15			5.9	4.9	2.9	0.0432
+1.9 kcal									

Values are for minimum energy conformers, unless otherwise shown. Atoms used for fitting are shown in brackets when they differ from the preceding molecule.

Fillers & Hawkinson 1982; Kaiser et al 1982; Ma et al 1982; Dandridge et al 1984). The structures of ATP and GTP were obtained from the program fragment file. 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronapthalene (ADTN), dopamine, dopexamine, NO-500, 2-amino-6-propyltetrahydrobenzothiazole (PTHB), LY-141865,

Table 3 Conformational analysis and molecular superimposition data for fitting dopamine agonists to adenosine triphosphate.

Molecule	Superimposed atomic distance (Å)			Torsion angles (°)		Intramolecular distance (Å)			RMS value
	N6	C2	O8			N6–O8	N6–C2	C2–O8	
ATP				C6-N9-C10-O9	−38	6.8	3.6	3.9	
				O9-C8-C7-O6	−59				
				C8-C7-O6-P3	170				
				C7-O6-P3-O2	−52				
				O6-P3-O2-P2	−71				
				P3-O2-P2-O11	34				
				O2-P2-O11-P1	−127				
				P2-O11-P1-O12	−80				
Dopamine +2.3 kcal	0.10	0.10	0.16	C2-C1-C7-C8	102	6.6	3.5	3.7	0.0080
				C1-C7-C8-N6	−80				
Dopexamine +2.4 kcal	0.09	0.18	0.17	C2-C1-C7-C8	−58	6.6	3.8	3.7	0.0234
				C1-C7-C8-N6	−72				
				C7-C8-N6-C9	−74				
				C8-N6-C9-C10	−170				
				N6-C9-C10-C11	−36				
				C9-C10-C11-C12	−57				
				C10-C11-C12-C13	152				
				C11-C12-C13-C14	−76				
				C12-C13-C14-N7	61				
				C13-C14-N7-C15	169				
				C14-N7-C15-C16	−161				
				N7-C15-C16-C17	−54				
				C15-C16-C17-C19	92				
Apomorphine	0.17	0.26	0.24			6.5	3.8	3.7	0.0583
S-Dihydroxy-nomefensine	0.23	0.12	0.21	C2-C1-C7-C8	−95	6.4	3.3	3.7	0.0117
				CI-C7-C8-N6	71				
R-Fenoldopam	0.13	0.25	0.18	C2-C1-C7-C8	57	7.0	3.3	4.2	0.0314

Values are for minimum energy conformers, unless otherwise shown. Atoms used for fitting are shown in brackets when they differ from the preceding molecule.

[2-(1*H*-indol-4-yl)-ethyl]-dipropylamine, GR218231, ester 33, haloperidol, L-745870, SCH23390 and zotepine were built from structures in the fragment file (Horn 1990; Ince 1990; Schaus & Bymaster 1998). Nitrogen atoms in agonists and antagonists corresponding to the protonated nitrogen atom of dopamine were designated as Nsp^{3+}. Conformational analysis was undertaken by rotating molecules about the bonds defined in Tables 1–4. It was considered that thermal energy would allow all conformers within 3 kcal of the minimum energy conformation to be valid. Molecules were fitted to ATP using three points of contact that incorporated the N2 and N6 atoms of GTP and ATP, respectively, and other atoms showing similarity of type, atomic distance and partial charge. With respect to the data for the agonists and antagonists in the figures and tables, atom N2 is equivalent to atom N6 and the designation depends on whether the fit relates to GTP (N2) or ATP (N6).

Results

The torsion angles describing the low energy conformers of GTP, ATP and the dopamine receptor agonists and antagonists used in this study are given in Tables 1–4. Figure 1 shows the superimposition of dopamine on the GTP molecule and the equivalent fitted atoms in the other dopamine agonists. D2-like receptor agonists and non-specific agonists all fit to hydroxyl O2 and O3 in the ribose ring and amino N2 in the guanine ring of GTP. The atomic distances N2–O2 (5.8 Å), N2–O3 (5.1 Å) and O2–O3 (2.6 Å) define a D2 pharmacophore in this GTP conformer. For the fitted dopamine agonists, the dimensions of the pharmacophore are 5.6–6.0 Å, 4.9–5.4 Å and 2.2–2.8 Å, respectively. All agonists, apart from [2-(1*H*-indol-4-yl)-ethyl]-dipropylamine, fit to this pharmacophore as minimum energy conformers. The fit of catechol hydroxyl groups is exclusive to the dopamine

Table 4 Conformational analysis and molecular superimposition data for fitting dopamine antagonists to adenosine triphosphate.

Molecule	Superimposed atomic distance (Å)			Torsion angles (°)		Intramolecular distance (Å)			RMS value
	N6	C2	O8			N6–O8	N6–C2	C2–O8	
ATP						6.8	3.6	3.9	
SCH23390	0.13	0.24	0.19	C3-C7-C8-C9	55	7.0	3.3	4.2	0.0330
			(C8)			(N6–C8)		(C2–C8)	
Clozapine	0.02	0.08	0.09	N12-C2-N11-C7	18	6.7	3.7	3.8	0.0039
Zotepine	0.07	0.19	0.14	C6-C2-O6-C9	−138	6.7	3.8	3.6	0.0069
+1.9 kcal				C2-O6-C9-C10	−179				
				O6-C9-C10-N6	−35				
				C9-C10-N6-C11	−74				
		(C7)	(C5)			(N6–C5)	(N6–C7)	(C7–C5)	
S-Sulpiride	0.22	0.16	0.11			7.1	3.9	3.8	0.0307
			(C4)			(N6–C4)		(C4–C7)	
Haloperidol	0.20	0.06	0.16	C1-C6-C7-C8	−178	6.5	3.4	3.8	0.0089
+3.0 kcal				C6-C7-C8-C9	92				
				C7-C8-C9-C10	80				
				C8-C9-C10-N6	−76				
				C9-C10-N6-C11	−68				
				C12-C13-C14-C15	41				
		(C12)	(C2)			(N6–C2)	(N6–C12)	(C2–C12)	
Trifluoperazine	0.22	0.16	0.12	C8-N1-C9-C10	−63	6.4	3.3	3.9	0.0305
+2.8 kcal				N1-C9-C10-C11	−78				
				C9-C10-C11-N3	128				
				C10-C11-N3-C1	160				

Values are for minimum energy conformers, unless otherwise shown. Atoms used for fitting are shown in brackets when they differ from the preceding molecule.

molecule although apomorphine and ADTN both possess a catechol ring. Ring C, N or S atoms substitute for catechol OH groups in [2-(1*H*-indol-4-yl)-ethyl]-dipropylamine, LY-141865 and PTHB. Ring C atoms in ADTN, apomorphine and NO-500 provide a closer fit to O2 and O3 (0.13 Å or less) than S and N atoms in LY-141865 and PTHB (0.18–0.24 Å).

The dopamine receptor antagonists in Figure 2 fit to the same D2 pharmacophore identified in the GTP conformer. Catechol rings are absent in all structures, which with the exceptions of GR 218231 and zotepine fit as minimum energy conformers. For the fitted dopamine antagonists, the dimensions of the pharmacophore (N2–O2, N2–O3, O2–O3) are 5.5–6.2 Å, 4.9–5.3 Å and 2.4–3.0 Å, respectively. In trifluoperazine, L-745870 and clozapine, ring N and C atoms substitute for catechol hydroxyl groups. Ring C atoms, methoxy and sulfoxide groups provide the same fit in sulpiride and GR218231. In haloperidol, ester 33 and zotepine, 2 ring carbon atoms substitute for the dopamine catechol hydroxyl groups. The fit of zotepine (see Figure 3) to GTP is not shown. All dopamine agonist and antagonist conformers listed in Tables 1 and 2 fit to the plane of the D2 pharmacophore in GTP with atom–plane distances of 0.0 Å.

D1-like receptor agonists and non-specific dopamine agonists define a pharmacophore in the low energy conformer of ATP, which incorporates hydroxyl O8 in the ribose ring, amino N6 and C2 in the adenine ring of ATP (Figure 3). The dimensions of the D1 pharmacophore in ATP are N6–O8 (6.8 Å), N6–C2 (3.6 Å) and C2–O8 (3.9 Å) (Tables 3 and 4). The dopamine conformer fitted to ATP is a more extended molecule than the minimum energy conformer fitted to GTP. For the D1 agonists and the antagonist SCH23390, the fitted atoms are of the same type as those in ATP. The OH group in the aforementioned molecules is replaced by a ring C atom in clozapine and zotepine. The inter-atomic distances representing the D1 pharmacophore in the fitted conformers (N6–O8, N6–C2 and C2–O8 in ATP) are 6.4–7.1 Å, 3.3–3.9 Å and 3.6–4.2 Å, respectively. Whereas clozapine and sulpiride fit to ATP as minimum energy conformers, the fits of haloperidol and trifluoperazine to ATP are not as good as those to the D2

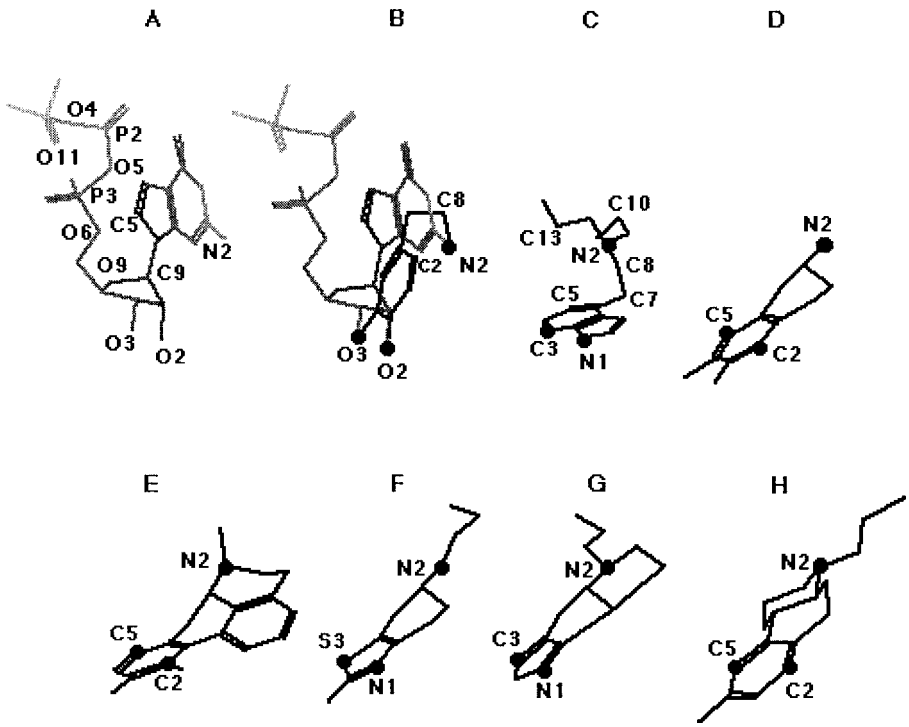

Figure 1 GTP (A); dopamine superimposed on GTP (B); dopamine agonists: [2-(1H-indol-4-yl)-ethyl]-dipropylamine (C), ADTN (D), apomorphine (E), PTHB (F), LY-141865 (G) and NO-500 (H), showing atoms fitted to GTP.

pharmacophore in GTP. The conformers of sulpiride, haloperidol and trifluoperazine are not shown, but relate to the structures in Figure 2. All dopamine agonists and antagonists listed in Tables 3 and 4 fit to the plane of the D1 pharmacophore in ATP with atom–plane distances of 0.0 Å.

Discussion

The rationale for fitting D1- and D2-like receptor ligands to the molecular structures of ATP and GTP lies in the established link between ligand–receptor mediated events and nucleotide changes in cells. Regulation of the D1 family of receptors is firmly linked to adenyl cyclase activity and the adenosine nucleotide (Missale et al 1998). The link between the D2 family of receptors and the guanosine nucleotide is long established, but features less prominently in the literature, for example the stimulant effect of D2 agonists on cGMP levels in mouse cerebellum (Gumulka et al 1976; Sethy et al 1996).

The development of various dopamine receptor models over the past 25 years is reviewed by Horn (1990). Grol et al (1985) postulate two binding sites complementary to the *p*- and *m*-hydroxyl groups of dopamine agonists, with two electronegative binding sites for the nitrogen atom. This model accounts for the activity of dopamine agonists with *m*-OH to N distances of 5.5–7.7 Å. In the present study, agonist OH–N distances fall within the 4.9–7.0 Å range and the *p*-OH group of dopamine features prominently in molecular fits to the nucleotides.

Data on the receptor-preferred conformation of dopamine is derived extensively from work on the planar agonists apomorphine and ADTN. The molecular species most commonly cited as the preferred dopamine conformation is the β-rotomer of the trans-b (co-planar) form. Comparative intra-atomic distances (Å) for this dopamine conformer and ADTN are N–O_α 7.8, N–O_β 6.8 and N–O_α 7.9, N–O_β 7.3, respectively, with a larger N atom–plane of benzene ring distance in dopamine (1.6 Å) than in ADTN (0.0 Å) (Horn 1990). This extended dopamine conformer does not relate well, however, to the molecular parameters of other known dopamine agonists. Fenoldopam, for example, is a highly effective dopamine agonist, despite not being able to attain the extended dopamine conformation. The N–O distance in the dopamine agonist 4-hydroxy-2-(dipropylamino) indan has been calculated at 5.5 Å (Hacksell et al 1981). Maximum bond lengths (Å) in

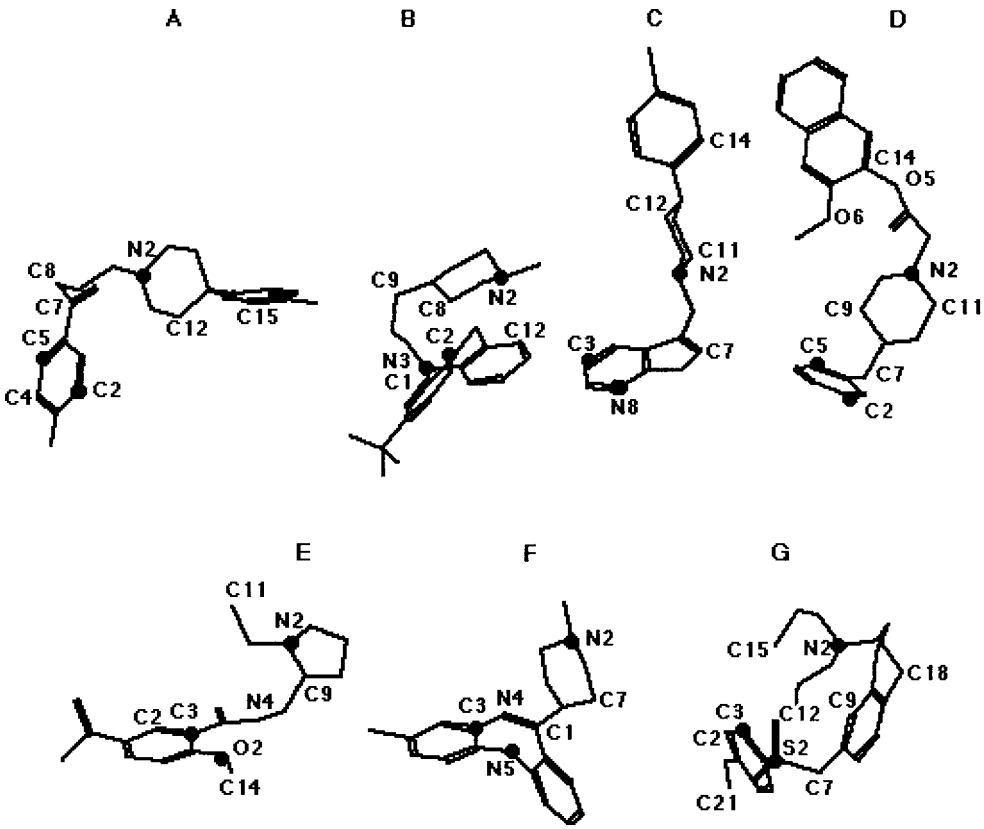

Figure 2 Dopamine antagonists: haloperidol (A), trifluoperazine (B), L-745870 (C), ester 33 (D), sulpiride (E), clozapine (F) and GR218231 (G), showing atoms fitted to GTP. The orientation of trifluoperazine differs to facilitate labelling.

other agonists used in this study that could correspond to the above dopamine N–O_α distance are PTHB 7.5, NO-500 7.4, [2-(1*H*-indol-4-yl)-ethyl]-dipropylamine 7.4, LY-141865 6.1. Furthermore, the free energy of the extended dopamine conformation exceeds that of the minimum energy conformer by 5 kcal. The dopamine conformers fitted to the ATP and GTP nucleotides are β-rotamers of the gauche form with N-plane benzene ring distances of 2.3–2.4 Å. The D2 pharmacophore, incorporating the catechol group of dopamine, relates as readily to the PTHB molecule and the catechol biostere rings of [2-(1*H*-indol-4-yl)-ethyl]-dipropylamine and NO-500 as it does to apomorphine and ADTN.

The fits of dopamine receptor ligands to the nucleotide structures take into account the functional groups of dopamine. The molecular structures in Figures 1–3 show that catechol, phenol, and free n-propyl side-chain groups are not essential for potent dopaminergic activity. Apomorphine and ADTN have a rigid phenethylene moiety. Pyrrole (LY-141865), pyrazole and indole ([2-(1*H*-indol-4-yl)-ethyl]-dipropylamine) rings function as catechol biosteres (Casy 1993) and are used in fits to the nucleotides. Dopamine and apomorphine fit best to the D2 pharmacophore identified in GTP, in terms of conformer free energy and closeness of fit, which is in keeping with the weaker activity of dopamine and apomorphine at D1-like receptors (DeMarinis et al 1986). The essential structural components of haloperidol for dopamine activity, the carbonyl function and 3-carbon chain of the butyrophenone (Horn 1990), are encompassed by the D2 pharmacophore.

The following stereochemical restrictions of dopamine receptor ligands (Casy 1993) are met in their fits to ATP and GTP. Apomorphine analogues, especially R-antipodes without a 10-OH group, behave as D1 antagonists; a preference reflected in the fit of the 11-OH group of apomorphine to ATP. The twentyfold preference of apomorphine for D2-like receptor sites is reflected in its superior fit to the D2 pharmacophore in GTP. D1-like receptor activity of the 3,4-catechol derivative of nomifensine resides in the *S*-enantiomer and

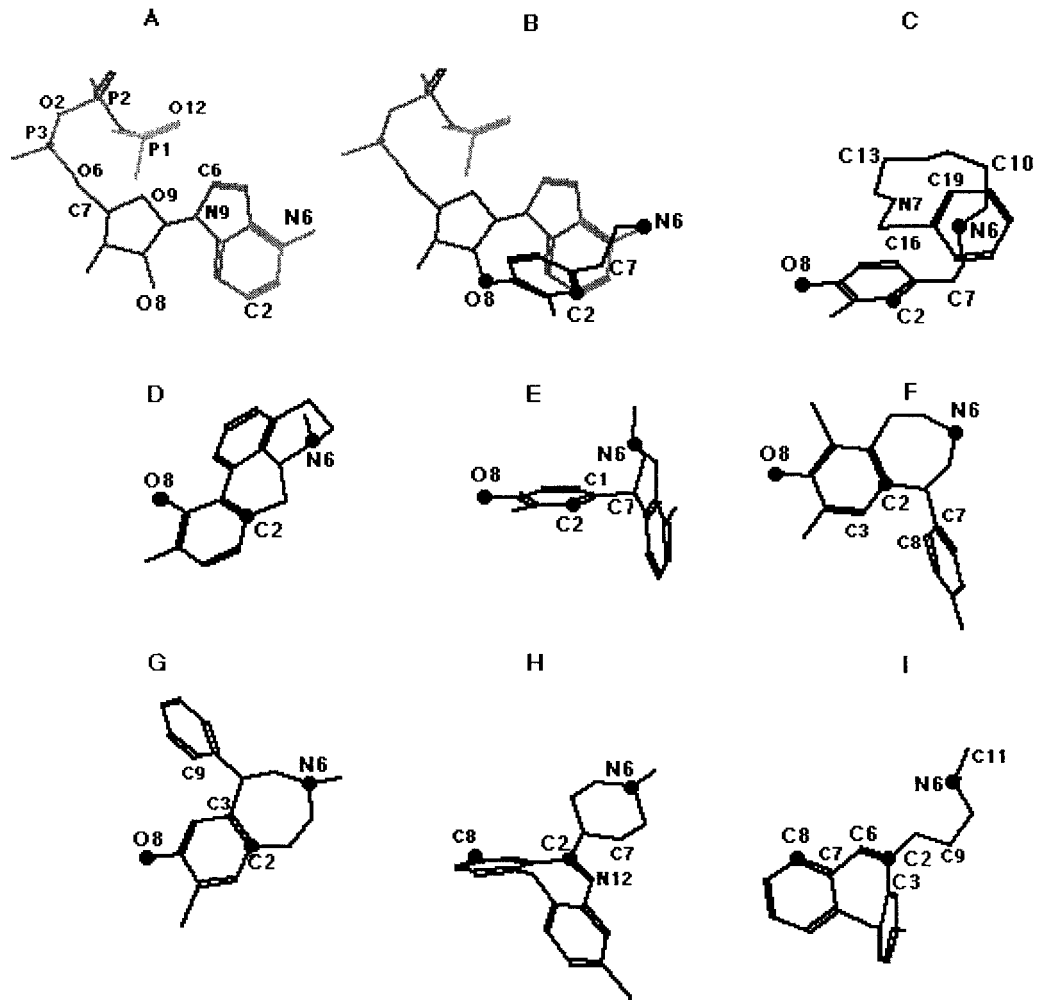

Figure 3 ATP (A); dopamine superimposed on ATP (B); dopamine agonists: dopexamine (C), apomorphine (D), dihydroxynomefensine (E), fenoldopam (F); dopamine antagonists: SCH23390 (G), clozapine (H) and zotepine (I), showing atoms fitted to ATP.

does not involve the amino substituent. Eutomers of the related phenylbenzazepine series, with agonist (fenoldopam) and antagonist (SCH 23990) activity, have a benzylic chiral centre of *R*-configuration. The eutomer of supiride has *S*-configuration. Thus, within the confines of our molecular superimposition data, the dopamine receptors ligands demonstrate a good fit to the ATP and GTP conformers.

Conclusion

The findings from this study are consistent with the idea that the dopamine receptor family, in common with receptor classes for other small molecular weight bioactive amines, may have evolved from a molecular template for the ATP and GTP nucleotides. The relative molecular similarity of neurotransmitter receptor ligands and purine nucleotides may shed some light, at a basic level, on receptor-mediated cyclic nucleotide changes, GTP- and adenosine-induced changes in receptor affinity, and the binding of atypical antipsychotic drugs to multiple neurotransmitter receptor classes.

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