Functional Analysis of the Human D2 Dopamine Receptor Missense Variants*

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The human dopamine D₂ receptor gene (DRD2) has three polymorphic variants that predict the amino acid substitutions Val⁹⁶ → Ala, Pro⁴¹⁰ → Ser, and Ser⁴¹¹ → Cys in the receptor protein. We have investigated the ligand binding and signal transduction properties of these human D₂ receptor variants by stably expressing them in cultured mammalian cells. The Cys⁴¹¹ and Ser⁴¹⁰ variants of the human D₂ receptor, which involve substitutions located in the third cytoplasmic loop, were markedly less effective in inhibiting cAMP synthesis than the most prevalent form (Pro⁴¹⁰ Ser⁴¹¹). Despite this difference, the Cys⁴¹¹ and Ser⁴¹⁰ variants couple to G proteins in CHO-K1 (Chinese hamster ovary) cells. The impairment of the Cys⁴¹¹ and Ser⁴¹⁰ variants to inhibit cAMP levels thus appears to result from a reduced ability of those variant receptors to activate the appropriate G₁ₛ-like protein. The demonstration of substantial functional differences between DRD2 gene variants found in the human population might have important pharmacological implications given the widespread use of D₂ receptor blocking drugs in the treatment of schizophrenia and other psychiatric disorders.

Dopamine receptors are members of a large superfamily of receptor proteins coupled to heterotrimeric guanine nucleotide-binding regulatory proteins (G proteins). The dopamine receptors are involved in motor control, neuroendocrine regulation, cognition, and emotion, and are crucial targets in the pharmacological therapy of schizophrenia, Parkinson’s disease, Tourette’s syndrome, tardive dyskinesia, and Huntington’s disease (1). Five human dopamine receptors have been identified to date (D₁, D₂, D₃, D₄, and D₅/D₁b), which are classified into two subfamilies (D₁-like and D₂-like). These two subfamilies have different pharmacologies, signal transduction properties, and genomic organization (2). The receptors of the D₁-like subfamily, D₁ and D₅, stimulate cAMP synthesis through coupling with G₁ₐ-like proteins, and their genes do not contain introns within their protein coding regions. Two of the members of the D₂-like family, D₂ and D₃, inhibit cAMP synthesis through their interaction with a G₁ₚ-like proteins and all members (D₂, D₃, and D₄) share a similar genomic organization, which includes introns within their protein coding regions (3).

Further diversity in the human dopamine receptors can be achieved by alternative RNA splicing and by the existence of expressed polymorphic sequences (1–3). For instance, the DRD2 gene can generate two alternative RNA splicing isoforms, D₂l (long) and D₂s (short), that differ by the presence or absence of a 29-amino acid sequence in the third cytoplasmic loop of the receptor protein (4, 5). The human DRD2 gene also has three identified DNA variants, which predict the amino acid substitutions Val⁹⁶ → Ala, Pro⁴¹⁰ → Ser, and Ser⁴¹¹ → Cys in the receptor protein (6). The prevalence of these DRD2 variants varies greatly in different human populations; in the Pima Native American population, the prevalence of the Cys⁴¹¹ DRD2 allele is as high as 16% (6), in the Japanese, the prevalence of Cys⁴¹¹ is 2.3% (7). In the Caucasian population the prevalence of the DRD2 variants was found to be 3% for Cys⁴¹¹ and 0.4% for Ser⁴¹⁰, with only one reported case for Ala⁹⁶ (1:392) (6, 8). Other human dopamine receptors also exhibit polymorphic variants. The D₄ receptor is the most polymorphic dopamine receptor with 20 different expressed variants identified to date (9, 10). Five polymorphisms coding for amino acid changes have been recently identified for the D₅ receptor (11), and the D₃ receptor is known to have one variant (12). No protein sequence variant has been identified for the D₁ receptor to date (13).

D₂ dopamine receptors are known to bind typical antipsychotic drugs with high affinity, and these drug affinities are correlated with clinical potencies in controlling psychotic symptoms in schizophrenia (14). Atypical antipsychotic drugs have been recently developed, which bind to serotonin as well as dopamine receptors; nevertheless, their improvement of positive psychotic symptoms has been suggested to result from blockade of D₂ receptors in the brain limbic system (15). If variations of the DRD2 sequence found in the human population are physiologically or pharmacologically relevant, they would be expected to change an associated biochemical variable, such as agonist and/or antagonist binding, interaction with G proteins, or signal transduction. For instance, the substitution in Ala⁹⁶ is located in the putative second transmembrane domain and therefore might be expected to affect the ligand binding pocket of the D₂ receptor, since residues in the second and other transmembrane domains have been shown to regulate ligand binding (reviewed in Ref. 16). Substitutions in the Ser⁴¹⁰ and Cys⁴¹¹ variants are located in the putative third cytoplasmic loop and might be expected to affect the interaction with G proteins, and therefore signal transduction, as studies with mutated G protein-coupled receptors have shown that this domain is a major determinant of G protein coupling (17, 18). Therefore, we have analyzed the ligand binding and signal transduction properties of the variants of the human D₂ receptor by expression in mammalian cell lines, which do not naturally express endogenous D₂ receptors.

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1 C. Armstrong, manuscript in preparation.
2 D. Goldman, personal communication.
Experimental Procedures

Mutagenesis, Cell Culture, and Transfection—A cDNA fragment coding for the short form of human D2 receptor (4) kindly provided by Dr. D. R. Grandy, Oregon Health Sciences University, Portland, OR was subcloned into the eukaryotic expression vector pSVK3 (Pharmacia Biotech, Upplands, Sweden) and used as a template for site-directed mutagenesis with the Transformer kit (Clontech Laboratories, Palo Alto, CA) using three different oligonucleotides containing the sequences from the Ala96, Ser310, and Cys311 variants. Confirmation of the mutations was obtained by DNA sequencing. For stable transfections, the four D2 receptor cDNA inserts were subcloned into pcDNA3 (Invitrogen Corp., San Diego, CA). African green monkey kidney (COS-7) and Chinese hamster ovary (CHO-K1)3 cells were cultured in Ham’s F-12 medium supplemented with 10% fetal bovine serum in a humidified atmosphere of 5% CO2 at 37 °C, and transfected with 30 μg of plasmid DNA using LipofectAMINE reagent (Life Technologies, Inc.). Stable transfected clones were selected in the presence of 1 mg/ml G418 (Life Technologies, Inc.). Positive receptor-expressing cell lines were identified by [3H]methylspiperone binding and maintained in culture with constant selection in the presence of 0.3 mg/ml G418.

Radioligand Binding Assays—Cells were harvested with 5 mM EDTA in Ca2+/Mg2+-free EBSS and centrifuged at 300 × g for 8 min. The cells were washed with EBSS, resuspended in 5 mM Tris, pH 7.4, at 4 °C, 5 mM MgCl2, and homogenized. Cell membranes were collected by centrifugation twice at 34,000 g for 20 min with an intermediate resuspension and were finally suspended in binding buffer (50 mM Tris-HCl, pH 7.4, 0.3% polyethylenimine). The filters were rapidly washed three times with 50 mM Tris-HCl, pH 7.4, and radioactivity bound to the filters was quantitated by scintillation counting using a [3H]cAMP assay kit (Diagnostic Products Corp., Los Angeles, CA).

Inhibition of Intracellular cAMP Synthesis by D2 Receptor Variants—The cDNAs encoding the human D2 receptor variants were initially tested by transient expression in COS-7 cells. Receptor densities in transiently transfected COS-7 cells ranged from 5.3 to 7.2 pmol/mg of membrane protein, as determined by [3H]methylspiperone binding. There were no differences between the variants with respect to the level of receptor expression or the affinities of the radioligand (data not shown).

In order to create stably transfected cells, CHO-K1 cells were transfected with the four D2 receptor cDNAs. Single G418-resistant clones were isolated and their D2 receptor expression characterized by [3H]methylspiperone binding. All D2 receptor-expressing CHO-K1 clones displayed saturable, concentration-dependent [3H]methylspiperone binding, with Kd values (mean ± S.E., n = 5) of 76 ± 12 pm for Ala96, 66 ± 7 pm for Ser310, 64 ± 7 pm for Cys311, and 73 ± 10 pm for the most prevalent D2 receptor variant (Val96, Pro310, Ser311) or “wild type” (Fig. 1). Thus, there was no significant difference between the variants and wild type receptor for [3H]methylspiperone binding (ANOVA, F(3,14) = 0.32, p = 0.80). For the purpose of further comparison among the different D2 receptor variants, G418-resistant clones expressing the D2 receptor variants were classified into two groups: low expression (0.4–0.7 pmol/mg of membrane protein) and high expression (1–2 pmol/mg of membrane protein). Both groups were further tested for regulation of cAMP synthesis inhibition and ligand binding.

Inhibition of Intracellular cAMP Synthesis by D2 Receptor Variants—We investigated whether the amino acid substitutions in the human D2 receptor variants result in a functional change in their ability to inhibit cAMP synthesis in CHO-K1 cells. The cell clones expressing the D2 variants showed no differences in basal cAMP levels (in picomoles per well): 0.33 ± 0.10 pmol for Ala96, 0.35 ± 0.08 pmol for Ser310, 0.34 ± 0.07 pmol for Cys311, and 0.36 ± 0.12 pmol for D2 wild type. After 15 min of treatment with 10 μM forskolin, a drug that stimulates adenyl cyclase, the intracellular cAMP levels were increased to 18.7 ± 2.3 pmol for Ala96, 19 ± 2.5 pmol for Ser310, 21.7 ± 1.8 pmol for Cys311, and 12.6 ± 0.3 pmol for D2 wild type. The forskolin-induced increase in cAMP levels could be reversed by dopamine in a concentration-dependent

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3 The abbreviations used are: CHO, Chinese hamster ovary; Gpp[NH]p, guanosine 5’-β,γ-mimiditrifosrophate; EBSS, Earle’s balanced salt solution; NMS, neuroleptic malignant syndrome.
manner (Fig. 2). With a maximal stimulation of 1 μM dopamine, the cAMP levels in forskolin-treated cells were 1.5 ± 0.4 pmol for Ala96, 4.9 ± 1 pmol for Ser310, 14.8 ± 2.9 pmol for Cys311, and 1.4 ± 0.3 pmol for D2 wild type (mean ± S.E., n = 5). Therefore, the wild type and Ala96 variant receptors were able to reduce the forskolin-induced cAMP levels to 7.6 ± 1.7% and 5.2 ± 2% of control, respectively (mean ± S.E., n = 5). In contrast, the variants Ser310 and Cys311 only reversed forskolin-induced cAMP levels to 24.3 ± 5.1% and 58.6 ± 10.5% of control, respectively (mean ± S.E., n = 5). The differences in the ability of the D2 receptor variants to reduce forskolin-induced cAMP levels were independent of their expression levels in the CHO-K1 cell clones. The variants Ser310 and Cys311 showed similar degrees of inhibition of cAMP levels when tested in cell clones expressing low (0.5 pmol/mg) versus high (1.5 pmol/mg) levels of the D2 variants. The EC50 values for dopamine to reduce forskolin-induced cAMP levels were 3 nM for Ala96, 2.3 nM for Ser310, 4.9 nM for Cys311, and 2.4 nM for D2 wild type (averaged data from five experiments). These data indicate that the substitution of a proline by a serine at position 310 and of a serine by a cysteine at position 311 of the human D2 receptor protein results in an impairment of the ability to inhibit intracellular cAMP levels upon dopamine stimulation.

Dopamine and [3H]Methylspiperone Competition Binding—Dopamine binding to the D2 receptor variants was initially tested by [3H]methylspiperone competition in the presence of 0.2 mM GTP, revealing single Kd values (mean ± S.E., n = 3) of 228 ± 26 nM for Ala96, 115 ± 23 nM for Ser310, 222 ± 28 nM for Cys311, and 120 ± 9 nM for the D2 wild type. Thus, the Ala96 and Cys311 variants exhibited approximately 2-fold lower affinities for dopamine than the Ser310 variant and D2 wild type receptor. These differences in Kd values for dopamine between the human D2 variants were also observed when the assays were performed in the reaction buffer containing sodium chloride (data not shown) and reached statistical significance (ANOVA, F(3,8) = 7.11, p = 0.012).

We next investigated the interaction of the human D2 receptor variants with G proteins present in the CHO-K1 cells by performing dopamine displacement of [3H]methylspiperone in parallel assays with and without 0.1 mM Gpp(NH)p and on membranes from cells treated with or without pertussis toxin. Gpp(NH)p and pertussis toxin both uncouple G protein-coupled receptors but through different molecular mechanisms. The nonhydrolyzable GTP analogue Gpp(NH)p binds to the α subunit of any G protein heterotrimer, causing permanent activation. Pertussis toxin catalyzes ADP-ribosylation of the α subunit of Gα, Gβ, and Gγ proteins, effectively blocking signal transduction. The conversion of two dopamine binding states (high and low affinity) to one state (low affinity) by both agents indicates the coupling of the D2 receptor variant to a G protein present in the CHO-K1 cells. Competition curves were analyzed using equations for displacement of radioligand and competitor to one and two binding sites. Results from curve fitting using a two-site model were retained when this model fit the data significantly better than a one-site model, as determined by an F test at a significance level of p < 0.05. Averaged data from eight dopamine competition curves of all human D2 receptor variants fit significantly better to the two-binding site model (Fig. 3). The D2 wild type receptor had 44% of the dopamine binding sites in the high affinity state with Kd = 7.9 ± 2.2 nM and a low affinity state with Ki = 403 ± 96 nM (mean ± S.E., n = 5). The Ala96 variant had 46% high affinity dopamine receptors with Kd = 11.7 ± 1.4 nM and a Kd = 607 ± 189 nM (mean ± S.E., n = 4), the Ser310 variant had 56% high affinity dopamine receptors with Kd = 13.5 ± 1.5 nM and a Kd = 617 ± 73 nM (mean ± S.E., n = 4), and the Cys311 variant had 47% high affinity dopamine receptors with Kd = 9.7 ± 3.3 nM and a Kd = 493 ± 67 nM (mean ± S.E., n = 5). Inclusion of 0.1 mM Gpp(NH)p in the reaction buffer resulted in dopamine competition curves with single Kd values of 228 ± 18 nM for Ala96, 212 ± 40 nM for Ser310, 417 ± 64 nM for Cys311, and 204 ± 32 nM for D2 wild type (mean ± S.E., n = 5). As previously observed, the affinity for dopamine of the Cys311 variant was about 2-fold lower than the affinities of the Ser310 variant and D2 wild type receptor. Similar experiments were performed after overnight treatment with 0.1 μg/ml pertussis toxin to identify the G proteins interacting with the D2 receptor variants. This treatment completely abolished the inhibition of forskolin-stimulated cAMP levels (results not shown). After pertussis toxin treatment, the single Kd values were: 297 ± 108 nM for Ala96, 288 ± 106 nM for Ser310, 380 ± 161 nM for Cys311, and 320 ± 131 nM for D2 wild type (mean ± S.E., n = 3).

DISCUSSION

We have analyzed the ligand binding and signal transduction properties of the human D2 receptor polymorphic variants Ala96, Ser310, and Cys311 expressed in cultured mammalian cells. The affinities of the Ala96, Ser310, and Cys311 variants for dopamine were approximately 2-fold lower than the affinities of the Ser310 variant and D2 wild type. No significant differences were detected in the binding affinity for the antagonist [3H]methylspiperone between the D2 wild type receptor and the expressed...
variants. Therefore, the amino acid changes in Ala96 and Cys311 seem to have a small effect on agonist but not antagonist binding. The amino acid substitution in Ala96 is located in the second transmembrane domain and could affect the ligand binding pocket of the D2 receptor. The substitution in the Cys311 variant is located in the third cytoplasmic loop, and some sequence changes in this receptor domain have been shown to shift agonist affinity without affecting antagonist binding (20). However, the differences in binding affinity for dopamine detected between some of the human D2 receptor variants are quantitatively small, and their biological significance is unknown.

We analyzed the modulation of cellular cAMP synthesis by the human D2 receptor variants as a model for signal transduction. The CHO-K1 clones tested had similar basal cAMP concentrations, which were greatly increased by forskolin treatment; this indicates that none of the amino acid substitutions in the D2 receptor variants results in a constitutive activation of the receptor. DopaminestimulationoftheD2 receptorvariantsandthewildtype receptor produced an inhibition of forskolin-stimulated cAMP levels in a concentration-dependent manner. Those changes in cAMP concentration are likely due to inhibition of adenylyl cyclase activity by a G-like protein coupled to the D2 receptor. There were marked differences in the ability of the different variants to inhibit cAMP synthesis. The D2 wild type and Ala96 variant receptors inhibited cAMP synthesis almost completely (to 6% of forskolin-stimulated cAMP levels). In contrast, the Ser310 and Cys311 variants were only able to inhibit cAMP synthesis to 24% and 58% of forskolin-induced levels, respectively (Fig. 2). These differences were observed in CHO clones expressing low levels (0.5–0.7 pmol/mg) and high levels (1–2 pmol/mg) of the human D2 receptor variants. These data also indicate that the results are not cell line-specific or are an artifact of the transfection process. Therefore the human D2 receptor variants with amino acid substitutions in the third cytoplasmic loop, Cys311 and Ser310, have an impairment in their ability to modulate adenylyl cyclase activity.

The interaction between the human D2 receptor variants and G proteins was further investigated with the use of Gpp(NH)p and pertussis toxin. No quantitative differences in coupling to G proteins expressed by the CHO cells were found between the D2 receptor variants and wild type. This G protein coupling was blocked by membrane incubation with Gpp(NH)p and by cell treatment with pertussis toxin. These data indicate that the impairment in inhibiting cAMP synthesis by the Cys311 and Ser310 variants is not due to a defect in G protein coupling but rather to a lower efficiency in activating the opioid subunit of the G protein heterotrimer. Activation of G protein-coupled receptors by an agonist induces a conformational change in the receptor, which is then able to activate the α subunit of the G protein (Gα). This activation is achieved by inducing a conformational change in the Gα subunit that decreases its affinity for GDP (reviewed in Ref. 21). The amino acid substitutions Cys311 and Ser310, located in the third cytoplasmic loop of the human D2 receptor, may render it less efficient in inducing the confor-
tional change required to activate Go.
An alternative explanation would be that the amino acid substitutions in the third cytoplasmic loop affect the G protein coupling specificity of the variant receptors. If the sequence changes in the Cys311 and Ser310 variants result in a fraction of these receptors coupling to Gα, their stimulatory effect on cAMP synthesis would decrease the inhibitory Gα-mediated effect. Coupling to a pertussis toxin-insensitive G protein (such as Gβ) would explain a lower Kᵢ for dopamine of the Cys311 variant after pertussis toxin treatment than in the presence of Gpp(NH)p (Fig. 3). To test this hypothesis, we performed cAMP assays after overnight cell treatment with 0.1 μg/ml pertussis toxin; under these conditions, Gα-mediated signal transduction is blocked while Gβ is unaffected. However, there was no detectable increase of cAMP synthesis by dopamine with any of the variants and wild type D2 receptors after pertussis toxin treatment without forskolin stimulation (results not shown).

The role of the diversity in dopamine receptor sequences in the human population poses an interesting question. It has been hypothesized that polymorphisms in dopamine receptors may correlate with individual differences in phenotype, including behavior, response to drugs, or susceptibility to disease. However, it cannot be predicted what effect, if any, a small functional change required to activate G protein-coupled receptors may have in the dopaminergic systems in the brain and on the behavior of an individual carrying such a variant. An association between D4 alleles and a human behavioral trait has recently been reported (22, 23). Variants of the human D4 receptor have been shown to have small differences in affinity for clozapine in the presence of sodium chloride, and in the EC₅₀ for dopamine to inhibit cAMP synthesis (10, 24). Those reported differences between D4 variants for inhibiting cAMP were smaller than the differences observed for the D2 variants Cys311 and Ser310.

Genetic associations between polymorphisms in the human DRD2 gene and several pathologies have been claimed, including alcoholism, polysubstance abuse, and schizophrenia (25–28). As several groups have failed to replicate them independently, those reports remain unconfirmed (6, 29–33). Mutations in G protein-coupled receptor genes have been shown to be the cause of several diseases. Mutations can cause receptor inactivation, as in the V2 vasopressin receptor in X-linked nephrogenic diabetes insipidus or constitutive activation as for rhodopsin in severe retinitis pigmentosa and congenital night blindness (reviewed in Ref. 34). Mutations in G protein-coupled receptors, although not implicated in a disease, could be associated with secondary effects to pharmacological treatment. For example, asthmatic patients who are homozygous for a mutation in the β₂ adrenergic receptor were found to be more likely to be steroid-dependent (35). In addition, the Ser310 variant of DRD2 was found in a patient with a clinical history of neuroleptic malignant syndrome (NMS) (8), and a larger series of patients with NMS is being investigated to establish whether this allele is associated with an increased susceptibility to NMS. Mutations in G protein-coupled receptors do not necessarily produce clinical pathology, e.g. the most common variation in human color vision is due to a polymorphism in the red opsin gene (36).

Given the allele frequencies of the DRD2 variants that predict amino acid substitutions in the human D2 receptor protein in the Caucasian population, most individuals carrying the variant receptors will be heterozygous. In those individuals, the co-expression of both alleles might complicate the evaluation of any pharmacological and behavioral effect that could be associated with a variant allele. However, in the Pima Native American population, the prevalence of the Cys311 DRD2 allele was found to be 16%, and other ethnic groups could also have higher frequencies of some of the DRD2 variant alleles. The potential effect of an impairment in D2 receptor signal transduction in the behavior or response to neuroleptic treatment in individuals expressing the Cys311 or Ser310 variants raises interesting questions that require further investigation.

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