

Differential Inhibition of 17 α -Hydroxylase and 17,20-Lyase Activities by Three Novel Missense CYP17 Mutations Identified in Patients with P450c17 Deficiency

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The microsomal enzyme cytochrome P450c17 is an important regulator of steroidogenesis. The enzyme has two functions: 17 α -hydroxylase and 17,20-lyase activities. These functions determine the ability of adrenal glands and gonads to synthesize 17 α -hydroxylated glucocorticoids (17 α -hydroxylase activity) and/or sex steroids (17,20-lyase activity). Both enzyme functions depend on correct steroid binding, but it was recently shown that isolated lyase deficiency can also be caused by mutations located in the redox partner interaction domain. In this article we present the clinical history and molecular analysis of two patients with combined 17 α -hydroxylase/17,20-lyase deficiency and four patients with isolated 17,20-lyase deficiency. In these six patients, four missense CYP17 mutations were identified. Two mutations were located in the steroid-binding domain (F114V and D116V), and the other two mutations were found in the redox partner

interaction domain (R347C and R347H). We investigated the activity of these mutated proteins by transfection experiments in COS-1 cells using pregnenolone, progesterone, or their hydroxylated products as a substrate and measuring 17 α -hydroxylase- and 17,20-lyase-dependent metabolites in the medium. The mutations in the steroid-binding domain (F114V and D116V) of P450c17 caused combined, complete (F114V), or partial (D116V) 17 α -hydroxylase and 17,20-lyase deficiencies, whereas mutations in the redox partner interaction domain (R347C and R347H) displayed less severe 17 α -hydroxylase deficiency, but complete 17,20-lyase deficiency. These findings are consistent with the clinical data and support the observation that the redox partner interaction domain is essential for normal 17,20-lyase function of P450c17. (*J Clin Endocrinol Metab* 87: 5714–5721, 2002)

IN THE STEROIDOGENIC pathway, cholesterol is converted into pregnenolone, which subsequently can be processed to either mineralocorticoids (no 17 α -hydroxylation) or glucocorticoids (17 α -hydroxylation) in adrenal glands or to sex steroids in adrenals and gonads (17 α -hydroxylation and 17,20-lyase activity). The microsomal enzyme cytochrome P450c17 is an important switchpoint in this steroidogenic pathway because it has both 17 α -hydroxylase and 17,20-lyase activities (Fig. 1). The first step necessary for P450c17 enzyme activity is steroid binding; then electron transfer occurs, enhanced by oxidoreductase to catalyze the hydroxylase reaction. The lyase activity is dependent on facilitation of the interaction of oxidoreductase with the redox partner-binding site (1). This interaction is enhanced by cytochrome b5 (2) or phosphorylation of phosphoserine residues (3). Optimal functioning of the redox partner-binding site is especially essential for the lyase reaction.

The P450c17 enzyme is encoded by the CYP17 gene, which is located on chromosome 10q24.3 (4). CYP17 gene mutations are known to cause either complete or partial, combined, or isolated 17 α -hydroxylase/17,20-lyase enzyme deficiencies. The study of these mutant enzymes found in patients with 17 α -hydroxylase/17,20-lyase enzyme deficiencies can help

us to understand the factors involved in P450c17 enzyme function. Until now 15 single base pair CYP17 gene mutations have been found, causing combined 17 α -hydroxylase and 17,20-lyase deficiencies (Table 1) (5–19). Only 2 mutations identified in patients with isolated complete 17,20-lyase deficiency were examined *in vitro* (Table 1) (14). These 2 mutations (R347H and R358Q) are located in the redox partner interaction domain. The observation of differential residual enzyme activity in naturally occurring mutations in various regions of the CYP17 gene supports the hypothesis that 17,20-lyase activity depends on normal function of the redox partner interaction site of the P450c17 enzyme (Fig. 1) (20).

In this article we present the clinical and molecular data of six patients with 17,20-lyase deficiency. In the CYP17 gene of these patients four different missense mutations were identified. Two mutations were located in the steroid-binding domain and two in the redox partner interaction domain. The effects of these four mutations on the enzymatic activity of the protein were examined by *in vitro* expression studies.

Subjects and Methods

Patients

The clinical picture and hormone levels of patient 1 have been described previously (21). This 17-yr-old female patient was referred be-

Abbreviations: AIS, Androgen insensitivity syndrome; DHEA, dehydroepiandrosterone; hCG, human chorionic gonadotropin; V_{max} , maximum velocity.

FIG. 1. Model of the mechanism of action of microsomal P450c17 and its differential regulation of 17-hydroxylase and 17,20-lyase activities. OR, Oxidoreductase; b5, cytochrome b5; e⁻, electron transfer [adapted from Auchus *et al.* (2)].

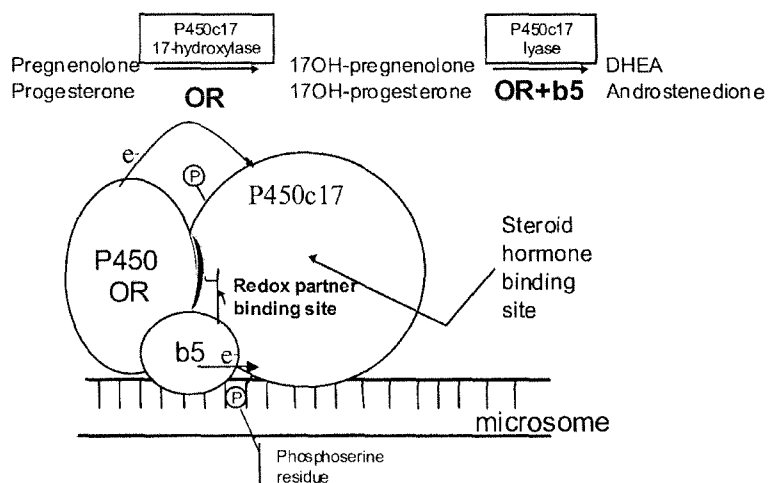


TABLE 1. All single base pair missense mutations in the *CYP17* gene described until now, their location, and their residual enzyme activity studied *in vitro*

Mutation	17 α -Hydroxylase (%)	17,20-Lyase (%)	Site of mutation ^a	Reference
R35L	38	33	Membrane	15
Y64S	15		Membrane	8
G90N	<1	<1		11
F93C	11	10	Steroid	19
R96W	25	25		12
S106P	<1	<1	Steroid	5
F114V	2.2	<1	Steroid	This article
D116V	37.7	10.7	Steroid	This article
N177D	10	10	Steroid	15
P342T	20	20		6
R347H	65	<5%	Redox	14
	44.1	<1		This article
R347C	13.6	<1	Redox	This article
R358Q	65	<5	Redox	14
H373L	<1	<1	Heme	9
P409R	<1	<1	Steroid	16
R415C	8	10	Heme(?)	18
F417C	<1	<1	Heme	13 and 14
R440H	<1	<1	Heme	10
R496C	<10	<10	Heme	7
R496H	38	33	Heme	15

^a Membrane, Membrane attachment domain; Steroid, steroid binding domain; Redox, redox partner interaction domain; Heme, heme binding domain; and Heme(?), uncertainty of affected domain (28).

cause of primary amenorrhea and lack of secondary sexual development (Tanner stage M1P1). She had one sister with normal secondary sexual development. The patient had female external genitalia, but no uterus and a 46,XY karyotype. Based on these results, the presumptive diagnosis of androgen insensitivity syndrome (AIS) was made. Secondary sexual development began after the start of estrogen substitution therapy. The patient underwent a hormonal evaluation before undergoing bilateral gonadectomy at the age of 20 yr. With the exception of fatigue, she had no complaints. Her blood pressure was elevated (150/110 mm Hg) despite low renin levels. Basal levels of androgens were low, and progesterone levels were high; basal cortisol was within the normal range, but rose insufficiently after ACTH (Table 2). These findings led to the diagnosis of combined 17 α -hydroxylase/17,20-lyase deficiency. Results of *in vitro* studies of testis tissue of this patient, using pregnenolone, 17-hydroxypregnenolone, and dehydroepiandrosterone (DHEA) as substrate, followed by measurement of metabolites confirmed the absence of 17 α -hydroxylase and 17,20-lyase activities (21).

Patient 2 is a 46,XY individual, who was born with an enlarged clitoris and no uterus. Her gonads were removed when she was 3 yr old. Based

on the combination of ambiguous genitalia, lack of pubic hair at puberty, low-normal levels of androgens, and cortisol (Table 2), combined partial 17 α -hydroxylase/17,20-lyase deficiency was diagnosed.

Patient 3 was born with complete female external genitalia and raised as a girl. She was the first child of consanguineous parents. The family history did not reveal any sexual differentiation disorders. At the age of 2 months, she had bilateral inguinal hernias, which contained testes, and subsequently, her karyotype was shown to be 46,XY. The presumptive diagnosis of AIS was made, and gonadectomy was performed. She was reevaluated at the age of 10 yr. Her blood pressure was 140/80 mm Hg despite normal renin levels. She underwent uneventful surgery twice. Basal levels of androgens were low, and progesterone was elevated. An ACTH test showed a low-normal basal level of cortisol that did not respond to ACTH (Table 3), suggesting partial 17 α -hydroxylase deficiency with complete 17,20-lyase deficiency.

Patient 4, raised as a girl, was evaluated at age 14 yr because of delayed puberty. She had a 46,XY karyotype and complete female external genitalia with an absent uterus. The presumptive diagnosis of AIS was made, and she underwent gonadectomy. At age 28 yr she was

TABLE 2. Serum hormone concentrations of patients 1 and 2 with *CYP17* mutations in the steroid binding domain

Hormone	Patient 1 (F114V) ^a		Patient 2 (D116V) ^a
	Basal	ACTH	Basal
LH (U/liter)	107.4 (1.5–9.4)		
FSH (U/liter)	38.4 (2.6–7.4)		
Progesterone (nmol/liter)	14.5 (0.5–2)	14.9	3.2 (0.5–2)
17OH-progesterone (nmol/liter)	0.29 (<10)	0.31	0.1 (<10)
Cortisol (nmol/liter)	220 (200–800)	240 (>500)	248 (200–800)
DHEA (nmol/liter)	<0.1 (3.5–25)	<0.1	3.6 (3.5–25)
Androstenedione (nmol/liter)	<0.1 (2–10)	<0.1	1.67 (2–10)
Testosterone (nmol/liter)	<0.2 (0.5–3)	<0.2	0.3 (0.5–3)
Renin (pg/ml)	<0.1 (0–2.5)	<0.1	

Normal age-adjusted reference values are shown in *parentheses*. In the ACTH test, venous catheters were inserted, and serum levels of several hormones were determined in blood samples taken before and at 60 min after the iv administration of 0.25 mg ACTH.

^a Age: patient 1, 17 yr; patient 2, 27 yr.

TABLE 3. Serum hormone concentrations of patients 3 and 4 with *CYP17* mutation R347C in the redox partner interaction domain

Hormone	Patient 3 (R347C) ^a		Patient 4 (R347C) ^a	
	Basal	ACTH	Basal	ACTH
LH (U/liter)	6.4 (<1)	5.4	10.6 (1.5–8)	
FSH (U/liter)	41.5 (<1)	46.5	37.3 (2–7)	
Progesterone (nmol/liter)	7.4 (0.5–2.0)	8.4	6.1 (0.5–2)	12.2
17OH-progesterone (nmol/liter)	2.4 (0.4–2.1)	2.6 (3.5–6.0)	1.9 (<10)	2.4
Cortisol (nmol/liter)	216 (200–800)	228 (>500)	232 (200–800)	285 (>500)
DHEA (nmol/liter)	0.3 (0.4–4.9)	0.5 (1.2–9.4)	0.0 (3.5–25)	0.0
Androstenedione (nmol/liter)	0.11 (0.24–0.8)	0.13 (0.4–1.6)	0.57 (2–10)	0.51
Testosterone (nmol/liter)	0.1 (<1)	0.1	0.1 (0.5–3.0)	
Renin (pg/ml)	12.5 (60–300)		10.2 (60–300)	

Normal age-adjusted reference values are shown in *parentheses*. The ACTH test is described in the legend to Table 2.

^a Age: patient 3, 10 yr; patient 4, 28 yr.

reevaluated. Her blood pressure was 170/90 mm Hg despite normal renin levels. She underwent surgery several times without complications. She developed breasts on estrogen substitution. Her main complaint was the complete absence of pubic hair, which developed with testosterone propionate ointment therapy. Basal levels of androgens were extremely low with elevated progesterone. She had low-normal basal levels of cortisol, which did not rise after ACTH stimulation (Table 3). These data are consistent with partial 17 α -hydroxylase deficiency and complete 17,20-lyase deficiency.

Patients 5 and 6 are siblings from consanguineous parents. Both 46,XY siblings were born with ambiguous external genitalia (Prader stage III). Patient 5 was assigned the male sex, and patient 6 was assigned the female sex on the basis of the sex designated by the parents at birth. There were no clinical signs of insufficient cortisol secretion. Both siblings underwent surgery several times without complications. Their basal serum levels of androgens were low and rose insufficiently after human chorionic gonadotropin (hCG) stimulation. Basal plasma renin activity was normal. Progesterone and 17-hydroxyprogesterone levels were high after hCG stimulation, and basal serum levels of cortisol were normal with some, but insufficient, rise during ACTH treatment (Table 4). On the basis of these observations the diagnosis of isolated 17,20-lyase deficiency was made.

Mutation analysis of the *CYP17* gene

Genomic DNA was isolated from leukocytes according to standard procedures (22). Exons 1–8 and their flanking intron sequences of the *CYP17* gene were amplified individually by PCR using the primers and PCR conditions described by Monno *et al.* (5), followed by single strand conformation polymorphism analysis (23) and sequencing of the fragments that showed abnormal single strand conformation polymorphism patterns. To determine whether two mutations identified in the same patient were on separate alleles, allele-specific amplification was carried out (patient 3), or DNA of the parents was sequenced (patients 1, 2, and 4).

Construction of mutant expression plasmids

Mutant *CYP17* expression plasmids were constructed using the conditions described previously for the LH receptor (24). pcDNA3 was used as the expression vector. For the exchange of fragments containing the mutation in the wild-type *CYP17* expression vector, flanking primers were used: T7 forward, AATACGACTCACTATAG; and 638 reverse, CTGTATGACATTCAACTC for the F114V and D116V mutants; and 670 forward, GCAAAGACAGCCTGGTGGACC; and SP6 reverse, CTATAGTGTACCTAAAT for the R347C and R347H mutations. The fragments were digested with the restriction enzymes *Bam*HI and *Bst*EII for the F114V and D116V mutants and *Bsp*EI and *Xho*I for the R347C and R347H mutations, respectively, and subsequently ligated into the expression vector that had been digested with the same enzymes. Primers that carry the mutation were as follows: F114V, GGGTATCGCCGTCGCTGACTCTG; D116V, CGCCTCGCTGTCTCCGGAGCACTGG; R347C, CAGTGACTGTAAATCGATTGCTCCTGCTG; and R347H, CCAACTATCAGTGATCATAACCGTCTC and their reverse complements.

Culture and transfection of cells

COS-1 cells were grown in 24-well plates to 50% confluence and transfected with 0.4 μ g/well (four wells per plasmid) of pcDNA expression plasmid containing wild-type or mutant *CYP17*. Transfection efficiency was monitored by cotransfection with a β -galactosidase expression plasmid. The transfected cells were washed and incubated in fresh medium. After 40 h when the COS-1 cells were 80–90% confluent, 1 μ M pregnenolone, progesterone, 17-hydroxyprogesterone, or 17-hydroxyprogesterone was added to the medium. After 8 h, *i.e.* during the period of linear steroid production against time (data not shown), the medium was removed and assayed for products using RIAs for 17-hydroxyprogesterone (DRG Diagnostics, Marburg, Germany) and DHEA or 17-hydroxyprogesterone and androstenedione (Diagnostic Products, Los Angeles, CA). All transfections were performed at least twice.

TABLE 4. Serum hormone concentrations of patients 5 and 6 with CYP17 mutation R347H in the redox partner interaction domain

Hormone	Patient 5 (R347H)				Patient 6 (R347H)			
	2 months old		7.5 yr old		2 wk old		2.5 yr old	
	Basal	hCG	Basal	ACTH	Basal	hCG	Basal	ACTH
LH (U/liter)	4.6 (2–12)				6.0 (2–26)			
FSH (U/liter)	2.9 (0–3.9)				4.7 (0–3.9)			
Progesterone (nmol/liter)	9.6 (0.5–2)		2.7 (0.5–2.0)	6.1			2.6 (0.5–2)	11.0
17OH-progesterone (nmol/liter)	4.5 (0.03–0.2)	14.9	1.3 (0.4–2.1)	1.5 (3.5–6)	13.4 (0.33–5.2)	19.6	1.3 (0.1–3.5)	2.1 (2.0–8.1)
Cortisol (nmol/liter)	194 (120–1158)	187	190 (157–414)	385 (>500)	270 (120–1158)	150	243 (157–690)	427 (>500)
DHEA (nmol/liter)	0.25 (0.9–8.2)	0.35	0.7 (0.4–4.9)	0.44 (1.2–9.4)	2.0 (0.9–8.2)	1.4	0.1 (0.3–1.5)	0.3 (0.7–3.3)
Androstenedione (nmol/liter)	0.14 (0.9–1.8)	0.15 (1.0–4.0)	0.10 (0.7–3.8)	0.09 (0.4–1.6)	0.3 (0.9–15)	0.4	0.07 (0.2–1.7)	0.05 (0.4–2.4)
Testosterone (nmol/liter)	0.7 (0.03–26)	4.1 (6.8–26)	0.02 (<0.5)	0.05	1.2 (0.03–26)	2.6 (6.8–26)	0.01 (<0.5)	0.09 (0.07–0.21)

Normal age-adjusted reference values are shown in parentheses. The ACTH test is described in the legend to Table 2. In the hCG test, serum hormone levels were determined in blood samples taken before and 72 h after the im administration of 1500 IU hCG.

In separate experiments, K_m and maximum velocity (V_{max}) were measured for the 17 α -hydroxylase and 17,20-lyase activities of the enzyme by culturing the cells in the presence of 0.1, 0.2, 0.5, 1, or 2 μ M pregnenolone or 17-hydroxypregnenolone, respectively, and measuring the concentration of the above-mentioned products using the same assays. Results were obtained with three or four wells of transfected cells per dose and were corrected for the concentrations measured in the medium of cells transfected with the empty vector.

Results

Mutations

The mutations identified in the CYP17 gene of our six patients are shown in Table 5. Mutation analysis of patients 1, 2, and 4 revealed compound heterozygosity for three novel mutations: F114V (TTC→GTC), D116V (GAC→GTC), and R347C (CGT→TGT), combined with a frameshift mutation on the other allele: a 4-base duplication near codon 480. This duplication has previously been observed in several families of Dutch and German Mennonite descent and is known to completely abolish all P450c17 enzyme activity (25). The novel mutations identified in patients 1 and 2 (F114V and D116V) are in the steroid-binding domain. Patient 3 was a compound heterozygote for two new mutations: R347C (CGT→TGT) and a 25-bp deletion in exon 1 (nucleotides 204–228 of the coding sequence, counting from the A of the start codon). This deletion renders the message out of frame, resulting in a premature stop codon located at 28 residues after the deletion. We therefore expect that this deletion in allele 2 does not lead to the production of any functional protein. Patient 4 showed the same R347C mutation in one allele, whereas the 4-bp dup exon 8 mutation that was also present in patients 1 and 2 was present in the other. The mutation R347C is located in the redox partner interaction domain. Localization of two different mutations identified in the CYP17 gene in patients 1–4 on separate alleles was confirmed by determining that each of their parents carried only one of these mutations (patients 1, 2, and 4) or by allele-specific amplification (patient 3). Finally, patients 5 and 6 (siblings) were homozygous for the R347H (CGT→CAT) mutation that has been described previously (14).

Expression of mutant proteins in COS-1 cells

The 17 α -hydroxylase and 17,20-lyase activities of the mutated proteins were estimated using transient transfection in COS-1 cells and compared with those of the wild-type enzyme. The conversion of various concentrations of pregnenolone to 17-hydroxypregnenolone and DHEA was used as a measure for 17 α -hydroxylase activity. Results are shown in Fig. 2A. Lineweaver-Burk plots calculated from these data are shown in Fig. 3. The r values for the regression lines were

TABLE 5. Mutations identified in the CYP17 gene of six patients

Patient	Allele 1	Site of mutation ^a	Allele 2
1	F114V	Steroid	4-bp duplication exon 8
2	D116V	Steroid	4-bp duplication exon 8
3	R347C	Redox partner	25-bp deletion exon 1
4	R347C	Redox partner	4-bp duplication exon 8
5 and 6	R347H	Redox partner	R347H

^a Steroid indicates steroid binding domain; redox partner indicates redox partner interaction domain (28).

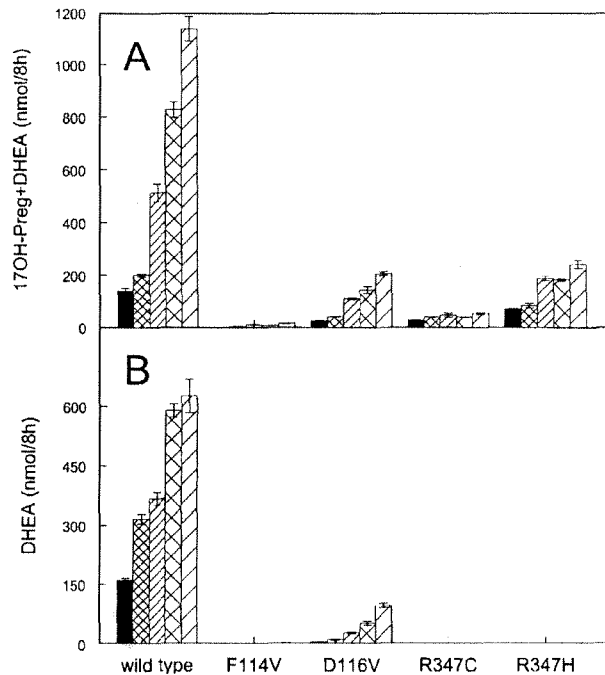


FIG. 2. Production of 17-hydroxypregnenolone (17OH-Preg) and DHEA after 8-h culture of transfected COS-1 cells in the presence of various concentrations of steroid precursors as a measure of 17 α -hydroxylase activity (A; culture with pregnenolone) and of 17,20-lyase activity (B; culture with 17-hydroxypregnenolone). The cells were transiently transfected with wild-type *CYP17* and the *CYP17* mutants. Substrate concentrations were 0.1, 0.2, 0.5, 1, or 2 μ M. Data are the mean \pm SEM ($n = 3$ in A and $n = 4$ in B).

all above 0.95. Resulting apparent values for K_m and V_{max} have been summarized in Table 6. All V_{max} values for the mutated proteins were lower than that for the wild-type protein, whereas K_m values of the proteins with mutations in the steroid-binding domain were comparable to that of the wild-type protein, and the K_m values for the other two proteins were lower. As an example for the separate amounts of 17-hydroxypregnenolone and DHEA produced, the data obtained with 1 μ M pregnenolone are plotted in Fig. 4. The use of a logarithmic axis allows a more clear indication of the amounts of DHEA. The wild-type enzyme and the F114V and D116V mutants converted between 10–20% of 17-hydroxypregnenolone to DHEA, whereas the R347C and R347H mutants did not produce measurable concentrations of DHEA despite the production of 17-hydroxypregnenolone.

Similar results were obtained using 17-hydroxypregnenolone as the substrate (Fig. 2B). Significant amounts of DHEA were only produced by the wild-type enzyme and the D116V mutant. The apparent V_{max} and K_m values for the wild-type enzyme were 1.55 min^{-1} and 0.35 μM , respectively. The production of DHEA by the mutated enzymes was too low to calculate V_{max} and K_m for the 17-hydroxypregnenolone to DHEA conversion by these enzymes. Conversion percentages at the highest concentration of 17-hydroxypregnenolone (2 μM) were 31.3%, 0.15%, 4.8%, 0.03%, and 0.12% for wild-type, F114V, D116V, R347C, and R347H, respectively.

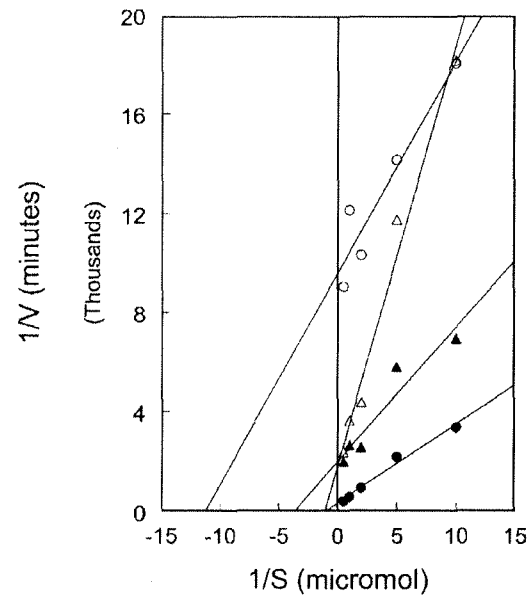


FIG. 3. Lineweaver-Burk plot for the conversion of pregnenolone to 17-hydroxypregnenolone plus DHEA, shown in Fig. 2A, by wild-type *CYP17* (●), and the D116V (Δ), R347C (○), and R347H (▲) mutants. Results for the F114V mutant are not shown, because all measured values are outside the axes used.

TABLE 6. Enzyme kinetic data on the 17 α -hydroxylase activity of the *CYP17* mutants investigated

	Wild type	F114V	D116V	R347C	R347H
K_m (μM)	0.97	0.76	0.95	0.08	0.27
V_{max} (min^{-1})	3.0	0.04	0.56	0.10	0.50

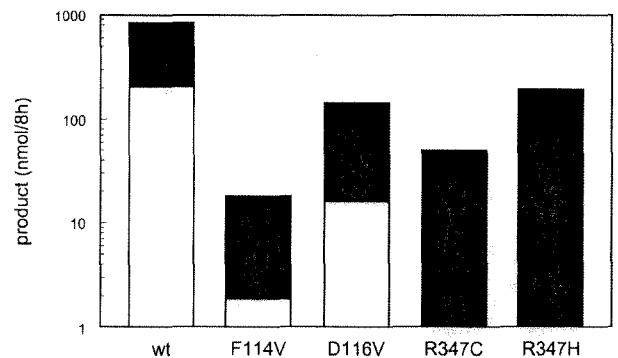


FIG. 4. Separate productions of 17-hydroxypregnenolone (■) and DHEA (□) from 1 μM pregnenolone by the COS-1 cells described in Fig. 2A. Note the logarithmic y-axis.

When progesterone was used as a substrate for testing the Δ^4 -steroid biosynthetic pathway, the production of 17-hydroxyprogesterone, indicative of hydroxylase activity, showed a similar pattern as the production of 17-hydroxypregnenolone from pregnenolone, but at lower levels (Fig. 5). With neither progesterone nor 17-hydroxyprogesterone (results not shown) as substrate did we observe significant production of androstenedione by the mutant

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