Association of Short-Term Response to Haloperidol Treatment With a Polymorphism in the Dopamine D_2 Receptor Gene

Martin Schäfer, M.D.
Dan Rujescu, M.D.
Ina Giegling
Axel Guntermann
Andreas Erfurth, M.D.
Brigitta Bondy, M.D.
Hans-Jürgen Möller, M.D.

Objective: Pharmacogenetic influences on therapeutic response to neuroleptic treatment are poorly understood. This study investigates the association of response to short-term haloperidol treatment with a Taq I polymorphism in the DRD2 gene.

Method: Fifty-seven patients with acute psychosis were treated with haloperidol for up to 28 days. Improvement and response were measured by using the Positive and Negative Syndrome Scale. Forty-one patients were homozygous for allele 2, and 16 were heterozygous.

Results: Heterozygous patients showed a greater improvement in positive, but not in negative, symptoms on all treatment days than patients homozygous for allele 2. Differences in improvement of positive symptoms reached statistical significance on days 14, 21, and 28. On treatment day 14, 10 (62.5%) of 16 heterozygous patients had at least 50% improvement of positive symptoms, compared with 11 (28.9%) of 38 homozygous patients.

Conclusions: These results support the hypothesis that genetic variations in the DRD2 gene may influence the individual response to antipsychotics.

(Am J Psychiatry 2001; 158:802–804)

Pharmacogenetic factors for individual differences in response to antipsychotics are largely unknown. Several association studies have been performed for the atypical antipsychotic clozapine (1), but there is a very limited amount of pharmacogenetic data on the response to typical antipsychotics such as haloperidol (2). This potent antipsychotic has high affinity to dopamine D_2 receptors and is very efficient in the treatment of patients with acute psychotic states, especially when positive symptoms predominate. We hypothesized that individual variations in short-term response to haloperidol may be influenced by functional variations (polymorphisms) in the dopamine D_2 receptor gene. Therefore, we investigated the association of response to short-term haloperidol treatment with a Taq I polymorphism in the DRD2 gene. The Taq I polymorphism is thought to be associated with the number of spiperone binding sites, which may be of functional pharmacological relevance (3).

Method

Fifty-seven Caucasian patients were treated with haloperidol during an acute psychotic episode for a period of up to 28 days. The mean age of the patients was 33.8 years (SD=10.3); 36 were men, and 21 were women. The mean age of the patients at onset of the illness was 28.5 years (SD=9.2), the mean number of hospitalizations was 2.2 (SD=1.9), the mean duration of hospitalizations was 2.2 months (SD=3.0), and the mean dose of haloperidol was 11.0 mg/day (SD=6.2), prescribed according to clinical need. With the exception of levomepromazin, no other antipsychotic medication was permitted. Clinical response was determined by administering the Positive and Negative Syndrome Scale at baseline and at days 7, 14, 21, and 28. Response was measured as percentage improvement in Positive and Negative Syndrome positive and negative subscale scores and defined as 50% improvement over baseline.

After a complete description of the study to the subjects, written informed consent was obtained. Genomic DNA was extracted from blood samples and was used as a template for polymerase chain reaction amplification. The distribution of the Taq I polymorphism in the DRD2 gene was examined as described previously (4).

Differences between groups were tested by using unpaired t test (two-tailed), analysis of variance, general linear model with repeated measurements, and chi-square test. Pearson's correlation coefficient was used to correlate haloperidol doses with response. The level of statistical significance was set at $p<0.05$.

Results

The study group consisted of 57 patients: 26 (45.6%) with schizophrenia, 18 (31.6%) with brief psychotic disorder, eight (14.0%) with substance-induced psychotic disorder, and five (8.8%) with schizoaffective disorder. The distribution of the polymorphism in these patients was in accordance with that in literature (5). Forty-one patients (71.9%) were homozygous for allele 2, and 16 (28.1%) were heterozygous.

Genetic groups did not differ with respect to the distribution of diagnoses at baseline and on day 7 (χ^2=1.03, df=3, p=0.80), on day 14 (χ^2=1.12, df=3, p=0.78), on day 21 (χ^2=2.39, df=3, p=0.50), or on day 28 (χ^2=3.41, df=2, p=0.19). They also did not differ in age (t=0.55, df=55, p=0.59), sex (χ^2=1.66, df=1, p=0.24), age at onset of illness (t=1.48, df=55, p=0.15), number of hospitalizations (t=–0.35, df=55, p=0.74), or duration of hospitalizations (t=–0.48,

TABLE 1. Response of 57 Patients With Acute Psychosis to Haloperidol Treatment[a]

Day of Study and Response Category	Percent of Responders or Nonresponders, by Diagnostic Group				Analysis		
	Schizophrenia (N=26)	Brief Psychotic Disorder (N=18)	Substance-Induced Psychotic Disorder (N=8)	Schizoaffective Disorder (N=5)	χ^2	df	p
Day 7					4.58	3	0.21
Responders	25.0	37.5	25.0	12.5			
Nonresponders	53.7	29.3	9.7	7.3			
Day 14					4.56	3	0.21
Responders	33.3	33.3	14.3	19.1			
Nonresponders	51.5	33.3	12.1	3.0			
Day 21					5.68	3	0.13
Responders	42.8	38.1	4.8	14.3			
Nonresponders	70.6	17.6	11.8	0.0			
Day 28					1.91	2	0.39
Responders	60.0	40.0	0.0	0.0			
Nonresponders	72.7	18.2	9.1	0.0			

[a] Response was defined as improvement of at least 50% in the score on the positive subscale of the Positive and Negative Syndrome Scale.

df=51, p=0.65). There was no difference between genetic groups in duration of episode before treatment, categorized by less than 1 month, less than 3 months, and 3 or more months (χ^2=3.11, df=2, p=0.22). Haloperidol doses were comparable on day 7 (t=0.37, df=55, p=0.72), day 14 (t=–0.82, df=53, p=0.42), day 21 (t=–1.05, df=38, p=0.31), and day 28 (t=–0.49, df=20, p=0.63); mean daily doses were comparable throughout the study (t=–0.96, df=172, p=0.34).

At baseline, scores on the positive (t=–0.50, df=55, p=0.63) and negative (t=1.10, df=55, p=0.28) subscales of the Positive and Negative Syndrome Scale were not different between the two genotype groups. The diagnostic groups also did not differ in positive and negative values, respectively, at baseline: schizophrenia (t=0.39, df=24, p=0.70, and t=1.46, df=24, p=0.16), schizoaffective disorder (t=1.53, df=3, p=0.23, and t=0.76, df=3, p=0.51), brief psychotic disorder (t=–0.45, df=16, p=0.67, and t=0.02, df=16, p=0.99), and substance-induced psychotic disorder (t=–2.08, df=6, p=0.09, and t=–0.24, df=6, p=0.82).

The percentages of patients in each diagnostic group who were defined as responders (their score on the positive subscale of the Positive and Negative Syndrome Scale improved by at least 50%) did not differ (Table 1).

Haloperidol dose was not correlated with response on day 7 (responders: r=0.04, N=16, p=0.89; nonresponders: r=–0.21, N=41, p=0.18) and day 14 (r=–0.29, N=21, p=0.21; nonresponders: r=–0.14, N=32, p=0.45) but was negatively correlated for nonresponders on day 21 (responders: r=–0.15, N=21, p=0.53; nonresponders: r=–0.66, N=16, p=0.005) and day 28 (responders: r=–0.58, N=10, p=0.09; nonresponders: r=–0.85, N=10, p=0.002). Furthermore, doses did not differ between responders and nonresponders on day 7 (t=0.77, df=55, p=0.45), day 14 (t=1.03, df=51, p=0.31), day 21 (t=0.64, df=35, p=0.53), or day 28 (t=1.49, df=18, p=0.16). The dropout rate was not related to the last available haloperidol dose (F=1.38, df=2, 33, p=0.27). Reasons for dropout before day 28 were early remission (12 [29.3%] of 41 homozygous patients and six [37.5%] of 16 heterozygous patients), severe side effects (six [14.6%] homozygous patients and four [25.0%] heterozygous patients), or nonresponse (seven [17.1%] homozygous patients and one [6.3%] heterozygous patient).

Overall, we observed a better response to haloperidol treatment in the heterozygous group. The improvement in positive symptoms in this group was greater than the improvement in the homozygous group on all assessment days and attained statistical significance on days 14, 21, and 28 (Table 2). This effect was also seen after applying the general linear model with repeated measurements (F=4.37, df=1, 55, p=0.05). There were no differences between heterozygous and homozygous groups in negative symptoms (Table 2) (F=1.28, df=1, 55, p=0.27).

On treatment day 14, 10 (62.5%) of 16 heterozygous patients were responders, compared with 11 [28.9%] of 38 homozygous patients (χ^2=5.33, df=1, p=0.04, odds ratio=4.09, 95% confidence interval [CI]=1.19–14.01, sensitivity=0.48, specificity=0.82). On day 21, nine (81.8%) of 11 heterozygous patients were responders, compared with 12 (44.4%) of 27 homozygous patients (χ^2=4.42, df=1, p=0.07, odds ratio=5.63, 95% CI=1.02–31.10, sensitivity=0.43, specificity=0.88). On day 28, four (80.0%) of five heterozygous patients were responders, compared with six (37.5%) of 16 homozygous patients (χ^2=2.76, df=1, p=0.15, odds ratio=6.67, 95% CI=0.60–74.51, sensitivity=0.40, specificity=0.91).

Discussion

To our knowledge, this is the first study to show an association between the Taq I polymorphism in the DRD2 gene and response to short-term haloperidol treatment in psychosis. Heterozygous patients showed a greater relative improvement of positive symptoms than homozygous patients, and more heterozygous patients than homozygous patients were responders. Furthermore, although there was no difference in negative symptoms at baseline, Positive and Negative Syndrome Scale negative sum scores were lower in heterozygous patients during the first 3 weeks of treatment, supporting a better overall outcome. Both groups were comparable with regard to the confounding variables mentioned previously; other predictors, such as

TABLE 2. DRD2 Receptor Genotype and Changes in Positive and Negative Syndrome Scale Scores During Haloperidol Treatment of 57 Patients With Acute Psychosis

Subscale of Positive and Negative Syndrome Scale, Day, and Genotype	N	Score		Difference in Score Between Genotypes			Improvement in Score (%)[a]		Difference in Score Between Genotypes		
		Mean	SD	t	df	p	Mean	SD	t	df	p
Positive subscale											
Day 0				–0.50	55	0.63					
2/2	41	24.00	6.04								
1/2	16	24.88	5.81								
Day 7				0.97	55	0.34			–1.52	55	0.14
2/2	41	16.85	6.68				29.25	21.43			
1/2	16	15.00	5.96				38.82	21.08			
Day 14				1.81	52	0.08			–2.94	52	0.005**
2/2	38	15.29	6.37				34.36	23.30			
1/2	16	12.19	3.89				50.00	15.00			
Day 21				1.86	36	0.08			–2.32	36	0.03*
2/2	27	14.33	5.74				40.00	24.57			
1/2	11	10.91	3.08				55.13	14.84			
Day 28				1.57	19	0.14			–2.53	19	0.03*
2/2	16	14.31	5.53				40.68	25.76			
1/2	5	10.20	3.11				60.27	9.67			
Negative subscale											
Day 0				1.10	55	0.28					
2/2	41	22.59	9.10								
1/2	16	19.75	7.66								
Day 7				2.05	55	0.05*			–0.74	55	0.47
2/2	41	19.51	8.86				10.46	27.03			
1/2	16	15.44	5.72				16.52	29.65			
Day 14				2.38	52	0.03*			–1.04	52	0.31
2/2	38	18.34	8.73				14.61	31.97			
1/2	16	13.50	5.83				24.84	35.97			
Day 21				2.31	36	0.03*			–1.44	36	0.16
2/2	27	17.22	7.65				14.22	34.82			
1/2	11	11.27	5.92				32.85	39.63			
Day 28				1.24	19	0.23			–0.51	19	0.62
2/2	16	17.31	7.65				20.35	23.69			
1/2	5	12.60	6.43				27.48	37.74			

[a] Improvement measured from day 0.
*p<0.05. **p<0.01.

inadequate haloperidol blood levels or differences in the relative amount of reduced haloperidol, remain to be excluded.

The results in this study support the hypothesis that this polymorphism or, alternatively, another genetic variation that is in linkage disequilibrium, may influence short-term individual response to antipsychotics. It remains unclear whether delayed response might be influenced by this polymorphism. Even given the stringent study design with monotherapeutic treatment, the number of subjects studied was small; therefore, these potentially important observations must be replicated in independent samples.

Presented in part at the 12th European College of Neuropsychopharmacology Congress, London, Sept. 21–25, 1999, and the 11th World Congress of Psychiatry, Hamburg, Germany, Aug. 6–11, 1999. Received April 19, 2000; revision received Oct. 17, 2000; accepted Nov. 17, 2000. From the Department of Psychiatry, Ludwig-Maximilians-University, Munich. Address reprint requests to Dr. Schäfer, Charité, Humboldt-University Berlin, Department of Psychiatry, Schumannstr. 20/21, D–10117 Berlin, Germany; martin. schaefer@chante.de (e-mail).

Dr. Rujescu was supported by the Vanda and Theodore Stanley Foundation.

The authors thank Sebastian Dittert, M.D., and Benedict Amann, M.D., for clinical support, Christopher Murgatroyd for reviewing the manuscript, and Klaus Maag, M.D., Department of Epidemiology and Biostatistics, Ludwig-Maximilians-University, for statistical advice.

References

1. Masellis M, Basile V, Meltzer HY, Lieberman JA, Sevy S, Macciardi FM, Cola P, Howard A, Badri F, Nöthen MM, Kalow W, Kennedy JL: Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology 1998; 19:123–132
2. Hwu HG, Hong CJ, Lee YL, Lee PC, Lee SFC: Dopamine D_4 receptor gene polymorphism and neuroleptic response in schizophrenia. Biol Psychiatry 1998; 44:483–487
3. Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ: Allelic association of the D_2 dopamine receptor gene with receptor-binding characteristics in alcoholism. Arch Gen Psychiatry 1991; 48:648–654
4. Grandy DK, Zhang Y, Civelli O: PCR detection of the TaqA RFLP at the DRD2 locus. Hum Mol Genet 1993; 2:2197
5. Sander T, Ladehoff M, Samochowiec J, Finckh U, Rommelspacher H, Schmidt LG: Lack of an allelic association between polymorphisms of the dopamine D_2 receptor gene and alcohol dependence in the German population. Alcohol Clin Exp Res 1999; 23:578–581