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Clinical, Biochemical, and Hormonal Aspects of Treatment With Des-Tyr^1-Gamma-Endorphin in Schizophrenia

Wim M.A. Verhoeven, Jan M. van Ree, Herman G.M. Westenberg, Jean M. Krul, Gerrit J. Brouwer, Jos H.H. Thijssen, David de Wied, Herman M. van Praag, Dominique L.S. Ceulemans, and René S. Kahn

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Abstract. Des-tyr^1-γ-endorphin (DTγE) was administered intramuscularly in a dose of 1 mg/day for 10 days to 18 neuroleptic-free schizophrenic patients in a double-blind crossover design. Six patients showed either a slight or no antipsychotic response; seven patients showed a moderate antipsychotic response; and the remaining five patients showed a marked antipsychotic response. DTγE led to a decrease of plasma prolactin levels in patients treated with DTγE in the first period of experimental treatment as compared to those treated with placebo. Neither plasma levels of growth hormone and cortisol nor cerebrospinal fluid concentrations of homovanillic acid, 5-hydroxyindoleacetic acid, and 3-methoxy-4-hydroxyphenylglycol were affected by DTγE. Patients suffering from a hebephrenic or paranoid type of schizophrenia and those presenting relatively fewer negative symptoms were most susceptible to treatment with DTγE. These data confirm and extend previous findings that DTγE has antipsychotic properties in a number of schizophrenic patients.

Key Words. Schizophrenia, DTγE, monoamines, pituitary hormones.

The spectrum of behavioral activities of γ-endorphin (β-endorphin 1-17) and, especially, of the nonopiate γ-endorphin fragment des-tyr^1-γ-endorphin (DTγE; β-endorphin 2-17) in rats corresponds at least in part to that of neuroleptic drugs (De Wied et al., 1978). This observation suggests that DTγE or a closely related neuropeptide might be an endogenous substance with neuroleptic-like activity, although with a profile more specific than that of the currently used neuroleptic drugs. Further, disturbances in the β-endorphin fragmentation may contribute to the pathogenesis of schizophrenic psychoses (De Wied, 1978).

To test the above hypothesis, one open and two double-blind crossover studies were carried out. The studies involved a total of 23 patients suffering from relapsing

Wim M.A. Verhoeven, M.D., Ph.D., Herman G.M. Westenberg, Ph.D., Dominique L.S. Ceulemans, M.D., and René S. Kahn, M.D., are in the Department of Psychiatry; Jan M. Van Ree, M.D., Ph.D., and David de Wied, M.D., Ph.D., are in the Rudolf Magnus Institute for Pharmacology; and Jos H.H. Thijssen, Ph.D., is in the Department of Endocrinology, State University Utrecht. Jean M. Krul, M.D., and Gerrit J. Brouwer, M.D., are at Psychiatric Hospital "Het Groot Graffel" in Warnsveld, The Netherlands. Herman M. van Praag, M.D., Ph.D., was formerly in the Department of Psychiatry, State University Utrecht, and now heads the Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY, USA. (Reprint requests to Dr. W.M.A. Verhoeven, Department of Psychiatry, State University, Nicolaas Beetsstraat 24, 3511 119 Utrecht, The Netherlands.)

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schizophrenia or schizoaffective psychosis, a number of whom showed either a diminution or disappearance of psychotic symptoms during or shortly after treatment with 1 mg DTγE/day for 8-10 days (Verhoeven et al., 1979, 1981). In addition, DTγE significantly decreased plasma prolactin levels in a group of 10 drug-free schizophrenic patients (Verhoeven et al., 1981). Analysis of the clinical data suggested that a high dose level of previously used neuroleptics and a long duration of the last psychotic episode negatively influenced the response to treatment with DTγE. Furthermore, patients diagnosed as suffering from schizoaffective psychosis, depressed type or schizophrenia, residual type hardly responded to DTγE, while only a slight response was observed in patients with catatonic schizophrenia (Van Ree et al., 1980, 1982*c*).

The present study focuses on neuroleptic-free schizophrenic patients who were selected as good candidates for DTγE treatment on the basis of the outcome of previous studies. The following criteria were used in patient selection: (1) diagnosis of schizophrenia, hebephrenic, undifferentiated, or paranoid subtype , and schizoaffective psychosis, manic type; (2) history of treatment with a relatively low dose of neuroleptics and/or a relatively short duration of the recent psychotic episode.

Because brain monoaminergic systems have been implicated in the symptomatology and pathogenesis of schizophrenia (Matthysse, 1974; Van Praag, 1975; Meltzer and Stahl, 1976; Van Kammen, 1979; Crow, 1980*a*, 1980*b*) and neuroleptics have pronounced effects of these systems (Bowers, 1974; Van Praag and Korf, 1975, 1976), the influence of DTγE on brain monoaminergic systems was analyzed by two strategies. First, the levels of the monoamine metabolites homovanillic acid (HVA), 3-methoxy-4-hydroxyphenylglycol (MHPG), and 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) were determined. Second, the daily patterns of plasma levels of prolactin (PRL), growth hormone (GH), and cortisol were measured because the secretion of pituitary hormones is controlled, among others, by monoaminergic systems (De Wied and De Jong, 1974; Smythe, 1977; Brown et al., 1978; Clemens and Shaar, 1980; Beumont, 1981).

Methods

Subjects. This study included a group of 18 patients, of whom 15 were admitted to the Psychiatric University Clinic in Utrecht and three to the Psychiatric Hospital "Het Groot Graffel" in Warnsveld, The Netherlands. Criteria for inclusion in the study required that patients be suffering from schizophrenia (residual and catatonic subtypes being excluded) or schizoaffective psychosis, manic type (depressed type being excluded) according to two independent psychiatrists. Patients previously treated with high doses of neuroleptic drugs, i.e., more than five times the mean normal dose recommended for this type of psychosis (Van Praag, 1978), and/or with a recent psychotic episode of more than 2 years' duration were excluded from the study. Diagnoses were based on the Research Diagnostic Criteria (Spitzer et al., 1978), the course of illness (Van Praag, 1976), and the data obtained from a complete Present State Examination (PSE) interview, including analysis according to the CATEGO program (Wing et al., 1975). In addition, the schizophrenic patients were assigned subtype diagnoses based on *DSM-III* (American Psychiatric Association, 1980) and ICD-9 (World Health Organization, 1977) criteria. (See Table 1 for further details concerning the patient sample.)

Before treatment with DTγE, none of the patients had been able to function adequately in society; 11 patients were hospitalized and 7 were unemployed, socially inactive, and living either

at their parents' home or in a halfway house. Physical and neurological examinations revealed no abnormalities.

Medication. In the 14 medicated subjects, the neuroleptics were gradually discontinued over a period of 3 weeks. All subjects were free of neuroleptic medication 2 weeks before the study began. After a 1-week baseline period in the clinic, subjects received a single daily injection of 1 mg DTγE or placebo (saline) intramuscularly (i.m.) for 10 days in a double-blind crossover design (10 days DTγE, 10 days placebo). Thereafter all subjects received placebo injections for 5 days (single-blind). Injections were given at 8 a.m.

Symptom Assessments. In the baseline period, a complete PSE interview was conducted with all patients and recorded on videotape in 14 patients. Based on the information obtained, a 7-point Patient Symptom Specific Rating Scale (PSSS) was prepared for each individual patient. During the experimental period, symptoms were rated once daily except during the weekends. Ratings were done by the treating psychiatrist, who used the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962, 1976) and the PSSS. In addition, a second psychiatrist made daily (15 patients) or twice weekly (3 patients) assessments using the BPRS. Scores were based on the symptoms present at the time of rating (between 11 a.m. and 5 p.m.). The BPRS was also administered by both psychiatrists on the day before the start of the treatment period (baseline) and 10 days after the last placebo injection (day 35). In addition, the Clinical Global Impression Scale (CGIS) (Guy, 1976) was scored 10 days (day 35) after the last day of the treatment period by a nontreating psychiatrist. The clinical course of all patients was followed for at least 6 weeks after the end of the experimental period. If DTγE resulted in a moderate to marked and sustained reduction of psychotic symptoms, the course of the disease and the social functioning of the patients were followed for at least 6 months (nonblind).

Laboratory Data. Morning blood samples were taken before the treatment period and once weekly during the study. An electrocardiogram was performed on the same days. The blood samples were used to measure hemoglobin concentration, leukocyte and differential cell counts, liver function values (SGOT, SGPT, and alkaline phosphatase), kidney function values (urea and creatinine), and erythrocyte sedimentation rate. On day 8 of both the peptide and placebo treatment periods, blood was collected from 8 a.m. every hour for 10 hours for determination of plasma PRL, GH, and cortisol. Samples were drawn via repeated venipuncture. Measurements were performed using radioimmunoassays as previously described (Verhoeven et al., 1981). On day 9, CSF was collected at 10 a.m. by lumbar puncture. CSF concentrations of the dopamine metabolite HVA, the noradrenalin metabolite MHPG, and the serotonin metabolite 5-HIAA were determined by means of liquid chromatography in conjunction with electrochemical detection (Westenberg et al., unpublished data).

Data Analysis and Statistics. The effect of treatment with DTγE on psychopathological symptoms was assessed by calculating the mean daily BPRS scores completed by the two psychiatrists. To assess the overall effect of treatment, scores at the end of the treatment periods were used to calculate the difference between the response to placebo and that to DTγE of the individual patients. These differences were assessed by two-way analysis of variance (ANOVA) with repeated measures (BMDP2V computer program). Scores on day 9 of the treatment periods were used for this analysis since no scoring was performed on day 10 of the second treatment period. In addition, the mean daily BPRS scores were expressed as percentages of the baseline score (day 0) of each individual subject. Based on our previous findings (Verhoeven et al., 1981, 1982), a decrease of more than 20% of the total BPRS scores was considered a response to treatment. The differences between DTγE and placebo treatment during the first 10 days of the experimental period were analyzed by calculating the percentage of patients who responded to treatment on day 9 or 10 and tested using the χ^2 test. The maximal response to DTγE at the end of active treatment (day 9 or 10) or in the period after active treatment (up to day 35 of the experimental period) was used to divide the patients among four groups: (1) no response

Table 1. Sample characteristics

Patient Age[1]/sex	Schizophrenic subtype	Hallucinations[2]	Delusions[3]	Thought disturbances	Emotional flattening	Motor symptoms[4]	Course[5]
1. 28/M	Hebephrenic	-	+ H,I	+	+	-	2
2. 20/M	Paranoid	+ 0	+ I,P	-	+	-	1
3. 21/F	Hebephrenic	+ A,T	+ H,I,R	+	+	-	2
4. 31/F	Schizoaff. manic	-	-	+	+	-	2
5. 23/M	Hebephrenic	-	+ R	+	+	-	2
6. 21/F	Paranoid	+ A,V	+ I,R,P	+	+	-	4
7. 29/F	Paranoid	+ T	+ I,R	+	+	-	1
8. 25/F	Paranoid	+ A	+ R,P	-	+	-	2
9. 30/F	Hebephrenic	+ A	+ I	-	+	-	2
10. 23/F	Undifferentiated	+ ?	+ P	+	+	-	2
11. 28/M	Hebephrenic	+ A	+ I,Re,P	-	+	-	2
12. 30/M	Paranoid	+ A	+ I,Re,Gr	+	+	-	2
13. 21/M	Hebephrenic	+ A,T	+ I,Gr,Re	+	+	-	First episode
14. 19/M	Undifferentiated	+ A	+ H,R	-	+	-	First episode
15. 18/M	Hebephrenic	-	-	+	+	+ R	First episode
16. 40/F	Undifferentiated	+ A	+ R	-	+	-	2,3
17. 18/M	Paranoid	+ A	+ I,R,P	+	-	-	2
18. 27/M	Paranoid	-	+ I,R,P	+	-	-	2

1. In years.
2. A = auditory hallucinations; V = visual hallucinations; T = tactile hallucinations; O = olfactory hallucinations.
3. I = delusions of being influenced; R = delusions of reference; H = hypochondriacal delusions; Re = delusions of religion; Gr = delusions of grandiose identity; P = paranoid attitude.
4. R = retardation.
5. 1 = several episodes with recovery to premorbid level after each episode; 2 = several episodes with residual symptoms after each episode; 3 = chronic (duration >1 year), inadequate treatment; 4 = chronic although treatment presumed adequate.

Etiology[6]	Illness duration[1]	No. past hospital-izations	Neuroleptic treatment duration[1]	Last psychotic episode[7]	Neuroleptic medication (6 weeks)
1a	12	1	0.25	14	—
1a	2.5	1	0.33	3	Trifluoperazine 2dd 2mg
1c	3	3	1.5	5	Thioridazine 3dd 50mg
1a	9	4	5	4	Bromoperidol 1dd 15mg
1a	2.5	2	1.5	5	Trifluoperazine 2dd 50mg
1a	5	3	5	13	Flupenthixol dec., 40mg/w
1a 2	4	3	0.83	11	—
1a	4.5	3	4	3	Trifluoperazine 3dd 10mg
1b 2	11	3	5	8	Thioridazine vesp., 50mg Fluphenazine decanoate 50mg/2w
1a 2	6	3	3	6	—
1a	4	4	0.5	4	Thioridazine 4dd 100mg
1c	5.5	4	2	4	Bromoperidol 1dd 5mg
1a	1	0	0.17	8	Trifluoperidol 3dd 0.25mg
1a	2	0	0.33	24	Trifluoperazine 4dd 10mg
1b	1.5	0	—	10	—
1a	15	0	10	14	Haloperidol 2dd 1mg
1a 2	1.5	1	1	2	Trifluoperazine 2dd 20mg
1b	9	2	2	6	Pimozide 4dd 1mg Trifluoperazine 4dd 10mg

6. 1a = Premorbid personality manifestly neurotic; environmental precipitating factors clearly demonstrable. 1b = Premorbid personality not clearly disturbed; environmental precipitating factors clearly demonstrable. 1c = Premorbid personality not clearly disturbed; environmental precipitating factors not clearly demonstrable. 2 = Hereditary factors.
7. Duration in months.

(≤20%); (2) slight response (20-50%); (3) moderate response (50-80%); (4) marked response (≥80%). To avoid small samples, groups 1 and 2 (no or slight response) and groups 3 and 4 (moderate to marked response) were combined for the analysis of some data. In fact, more than 50% maximal response was taken as indicating improvement of clinical significance. Blood levels of PRL, GH, and cortisol were calculated as mean ± SD and additionally analyzed by assessing the area above the daytime curve (AAC) for each individual subject. CSF levels of the monoamine metabolites were calculated as mean ± SD (HVA and 5-HIAA) or as median (MHPG). Statistical analyses were performed using Student's *t* test (HVA and 5-HIAA) or Mann-Whitney *U* test (MHPG).

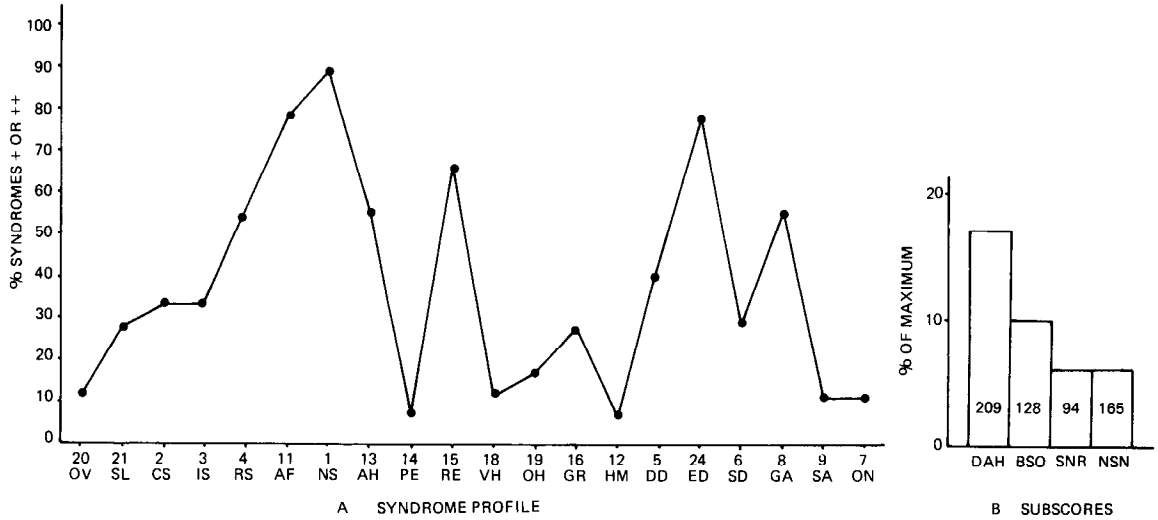
Results

Diagnosis. With respect to the syndromes of the patients as assessed by CATEGO, one patient (1) was classified as psychotic depression (subclass PD^+; class D^+). The other 17 patients all belonged to the class of schizophrenic psychoses (S^+) and subclass nuclear schizophrenia (NS^+). With respect to clinical classification, the reliability of the PSE data was high, since the Index of Definition (ID) was 8 in 13 patients, 5 in 2 patients (4 and 5), 6 in 2 patients (2 and 14), and 7 in 1 patient (16). The PSE profile (see Fig. 1) accords well with that obtained by others for schizophrenic patients (Cooper et al., 1972; World Health Organization, 1973; Wing et al., 1975; Verhey, 1981) except for the rare occurrence of delusions of persecution (PE; syndrome 14). Patients with such syndromes were excluded from the study because of their extremely paranoid behavior. Thus, the PSE data indicate that all but one of the patients (1) were suffering from nuclear schizophrenia.

Clinical Data. The mean total BPRS score (± SEM) of the patients receiving neuroleptics 4 weeks before the experimental period was 22.4 ± 1.9 and at the start of the study 24.8 ± 1.8. In five patients an increase in psychotic symptoms >20% occurred after discontinuation of neuroleptics, in two a slight decrease occurred, and in the remaining 10 patients psychotic symptoms hardly changed (<20% of the score before discontinuation of neuroleptics). In 10 patients (2, 3, 5, 8, 10, 13, 14, 15, 16, and 18) treatment was started with DTγE for 10 days, followed by 10 days of placebo. In the other eight patients the treatment schedule was reversed. Statistical analysis of scores at the end of the treatment periods revealed that there was a significant sequence effect ($F = 37.6$; $df = 1, 16$; $p < 0.001$), but no significant interaction between sequence and treatment ($F = 0.01$; $df = 1, 16$; $p > 0.05$). A significant treatment effect was obtained: scores at the end of DTγE treatment were lower than after placebo treatment ($F = 7.39$; $df = 1, 16$; $p = 0.015$). The mean (± SD) BPRS scores of the patients were 22.6 ± 7.7 and 20.4 ± 9.0 on day 9 of the first treatment period and 17.0 ± 8.7 and 14.0 ± 5.6 on day 9 of the second treatment period for placebo- and DTγE-treated patients, respectively. Six out of 10 patients who started with DTγE during the first treatment period responded to treatment (assessed on day 9 or 10 of treatment), while the eight placebo-treated patients did not respond ($p < 0.02$; χ^2 test). All eight patients responded to DTγE in the second treatment period.

When each patient's response to treatment was expressed as a percentage of the baseline BPRS scores, no response was found in one patient (10), a slight response in five patients (7, 8, 14, 15, 16), a moderate response in seven patients (1, 2, 3, 6, 11, 12, 13), and a marked response in five patients (4, 5, 9, 17, 18). Since a response >50% was

Fig. 1. PSE syndrome profile and subscores of schizophrenic patients (n = 18) in the DTγE study



A. The 20 syndromes are plotted vs. the percentages of patients with the syndrome with a score of + or ++.
B. The 4 PSE subscores of the 18 patients, as derived from the PSE, are expressed as percentages of the theoretical maximum scores. Figures in vertical bars indicate absolute values of subscores.
DAH = delusional and hallucinatory syndromes; BSO = behavior, speech, and other syndromes; SNR = specific neurotic syndromes; NSN = nonspecific neurotic syndromes. For details concerning the PSE and CATEGO program, see Wing et al. (1975).

taken as indicating clinically significant improvement, the patients were divided into two groups (see Fig. 2). Scores on five BPRS subscales for responders showed no marked differences among the five symptom groups, either in degree of improvement shown or in the time course of improvement. Overall analyses and ANOVAs of the data of all patients obtained on day 9 of the treatment periods revealed that a significant sequence effect was present in the case of the HOST ($F = 8.32$; $df = 1, 16$; $p = 0.01$), THOT ($F = 8.9$, $p = 0.0005$), ANER ($F = 4.81$, $p = 0.043$), and ACTV scales ($F = 37.0$, $p < 0.001$) but not of the ANDP scale ($F = 1.98$, $p = 0.18$).No interaction was present between sequence and treatment in any of the subscales. A significant treatment effect was obtained in the case of the ANDP ($F = 4.65$, $p = 0.047$) and ACTV scales ($F = 25.9$, $p < 0.001$), and a tendency toward a treatment effect was found in the case of the THOT ($F = 2.30$, $p = 0.15$) and ANER scales ($F = 1.98$, $p = 0.18$). No treatment effect was present on the HOST scale ($F = 0.45$, $p = 0.31$), presumably due to an increase of symptoms belonging to this scale in one patient on day 9 of peptide treatment.

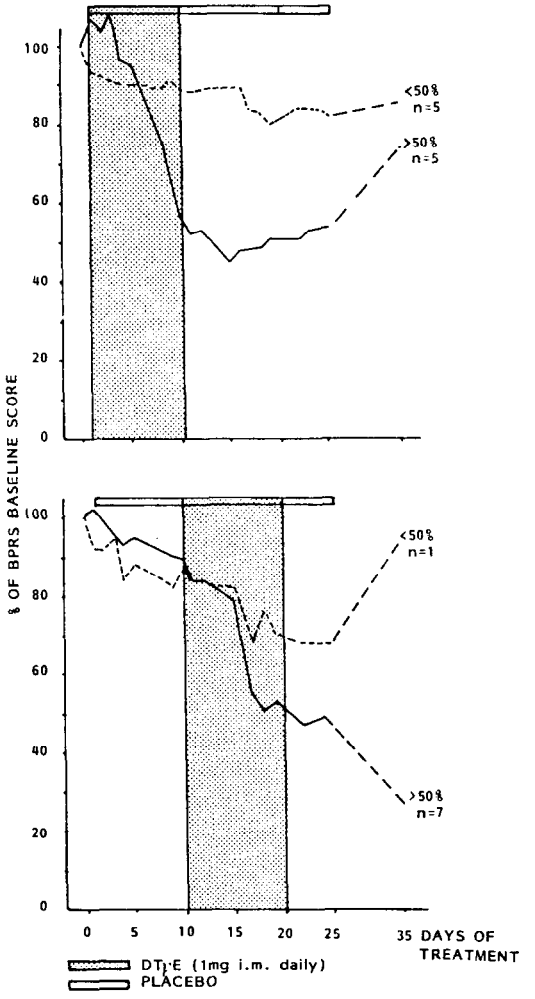
The PSSS scores revealed results generally similar to those on the BPRS. In fact, a close correlation ($r = 0.90$) was observed between the results with both rating instruments. A fairly good relationship was also found between the effect as assessed with the BPRS and the clinical efficacy as indicated on the CGIS.

Course of Illness After DTγE Treatment. Before treatment with DTγE, all patients showed persistent psychotic symptoms despite neuroleptic medication, and none of them were able to function adequately in society.

In the 12 patients showing a moderate to marked response, the decrease in psychotic symptomatology began on days 4-8 of active treatment. After the experimental period, neuroleptic medication was not reinstituted. In four of these patients (2, 3, 17, 18), the reduction of psychotic symptoms was temporary; they relapsed at the end of DTγE treatment or shortly thereafter (within 1 month). Four patients (6, 9, 11, 13) relapsed after 3 months, and one patient (12) relapsed after 6 months. In one patient (1), symptoms did not increase during the neuroleptic-free followup period of 12 months, while in two patients (4, 5), the psychopathological symptoms did not recur in that period. These latter patients functioned adequately in society at their premorbid level. In three relapsing patients (3, 6, 17), a second (double-blind) treatment period with DTγE was instituted as follows: 5 days placebo; 10 days 1 mg DTγE; 5 days placebo. The response in patient 3 was 45%, and subsequently she was treated with conventional neuroleptics. Patient 6 responded neither to the second DTγE treatment nor to clozapine and only partially to conventional neuroleptics. The response (86%) of patient 17 was quite similar to that observed during the first DTγE treatment; the same reduction of psychotic symptoms occurred.

Patient Characteristics Relevant to DTγE Response. Analysis of the PSE data revealed that patients with a response <50% ($n = 6$) showed significantly more symptoms belonging to the residual syndrome (RS; syndrome 4) as compared to patients with a response >80% ($n = 5$) ($p < 0.025$, Student's t test). Also, the BSO subscore was significantly higher ($p < 0.05$, Student's t test) in the group of patients with a response <50% as compared to those with a response >80%.

Fig. 2. Effect of DTγE on psychotic symptoms ($n = 18$)



Data are presented as mean percentage decrease of the BPRS baseline score vs. day of treatment for the patients who received DTγE (1 mg/day i.m.) during the first 10 days (top) or during days 10-20 (bottom). A double-blind crossover design was used. Patients of both treatment conditions were divided into 2 groups according to maximal response < or > 50%.

For the analysis of the BPRS baseline data, the scores of the negative symptoms (emotional withdrawal, motor retardation, blunted affect) were added for each individual subject. The same was done for the positive symptoms (conceptual disorganization, grandiosity, suspiciousness, hallucinatory behavior, unusual thought content). The intensity of the negative symptoms was more severe in the patients who responded <50% as compared to those with a response >80% ($p < 0.025$; Student's t test). With

respect to the positive symptoms, no differences were found between the two response groups.

When results were considered with respect to Research Diagnostic Criteria or *DSM-III* subtypes, the antipsychotic effect was found to be most pronounced in patients suffering from the hebephrenic and paranoid types of schizophrenia and in the patient with a schizoaffective psychosis, manic type, while the patients diagnosed as suffering from an undifferentiated type showed less response (Table 2).

The duration of the last psychotic episode was >10 months in six patients (four with a response <50% and two with a response >50%), while in 12 patients this period was <10 months (two with a response <50% and 10 with a response >50%). Thus, the response was more pronounced in patients whose last psychotic episode was <10 months in duration ($p < 0.05$, χ^2 test).

Hormonal Data. Blood was collected from 15 patients on 1 day during both placebo and DTγE treatment periods. Treatment began with DTγE in eight patients and with placebo in seven patients. For the first period of experimental treatment, no marked differences in plasma levels of GH and cortisol emerged between DTγE- and placebo-treated patients. The same held true for the second period of experimental treatment (data not shown). Analysis of the AAC (area above the daytime curve) of the individual patients also failed to reveal statistically significant differences between DTγE and placebo when data for both treatment periods were combined: differences and 95% confidence limits, GH: -8 (-32 to 16), cortisol: -0.24 (-0.92 to 0.44). In patients treated with DTγE in the first experimental period, the daytime PRL profile was lower compared to that of the placebo group (Fig. 3); but due to a marked variation between subjects, this decrease, as assessed with the AAC, did not reach statistical significance. However, the mean of plasma PRL levels obtained in the first 5 hours of the day was significantly lower in the DTγE group as compared to the placebo group ($p < 0.05$, Student's t test). In the second experimental treatment period, a complicated picture emerged with respect to plasma PRL levels; DTγE resulted in a slight decrease in PRL levels as compared to placebo treatment in the first period. Patients treated with DTγE followed by placebo had low plasma PRL levels in both periods of experimental treatment, a finding which may suggest that DTγE treatment leads to a sustained decrease of plasma PRL. Due to these effects and the marked variation between subjects, the AACs during DTγE were not significantly different from those during placebo treatment when the data from both treatment periods were combined: difference and 95% confidence limit, -0.18 (-0.62 to 0.26).

Monoamine Data. In 14 patients CSF was collected in both placebo and DTγE treatment periods. In seven patients treatment began with DTγE and in the other seven patients with placebo. No significant changes in the CSF levels of HVA, 5-HIAA, and MHPG were observed during DTγE treatment as compared to placebo treatment, regardless of whether the data were analyzed between or within subjects (Table 3). A slight, nonsignificant increase of MHPG levels was observed during DTγE as compared to placebo treatment, but only in the first treatment period.

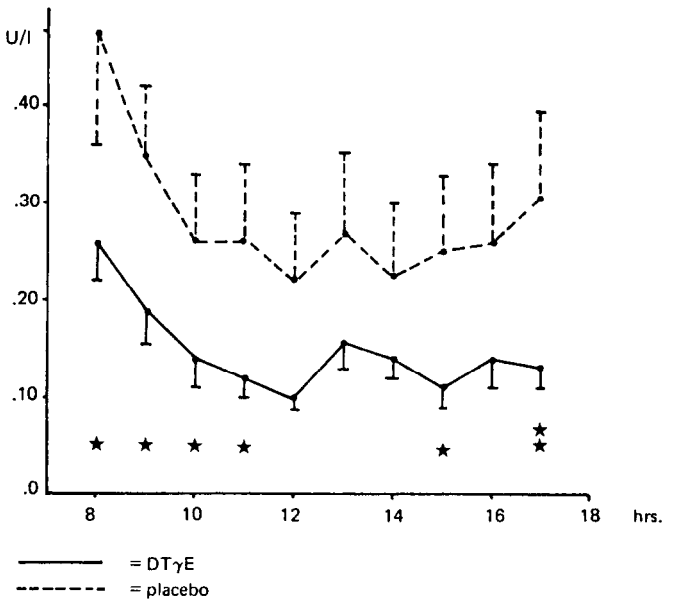
Laboratory Data and Side Effects. DTγE did not cause changes in any of the hematological and biochemical laboratory data. The electrocardiogram showed no

Table 2. Maximal posttreatment decrease in BPRS symptom scores

	Baseline BPRS score	Minimal BPRS score	Response % BPRS				
Diagnosis	**Mean ± SD**	**Mean ± SD**	**<20**	**20-50**	**50-80**	**>80**	**Mean ± SD**
Hebephrenic ($n = 7$)	27.0 ± 9.6	11.1 ± 6.9	—	1	4	2	60.9 ± 24.8
Paranoid ($n = 7$)	22.6 ± 5.1	8.8 ± 4.7	—	2	3	2	61.3 ± 21.2
Undifferentiated ($n = 3$)	27.7 ± 6.1	22.0 ± 9.2	1	2	—	—	22.3 ± 16.8
Schizoaffective manic ($n = 1$)	16.5	1	—	—	—	1	94.0
Total ($n = 18$)	24.8 ± 7.4	11.5 ± 8.0	1	5	7	5	56.4 ± 26.7

changes. DTγE was not associated with extrapyramidal side effects, and no cardiovascular or gastrointestinal complaints were reported. Injections did not cause local effects.

Fig. 3. Influence of DTγE on plasma levels of prolactin (U/l) in schizophrenic patients



Data are presented as mean ± SEM vs. hours of the day. Blood samples were collected from 8 a.m. every hour for 10 hours on day 8 of placebo or peptide treatment (1st period of experimental treatment). Solid lines: DTγE (n = 8); broken lines: placebo (n = 7).
*$p < 0.1$, Student's t test.
**$p < 0.05$, Student's t test.

Table 3. Influence of DTγE on CSF concentrations of HVA, 5-HIAA, and MHPG

	Treatment conditions			
	1. DTγE	2. Placebo	1. Placebo	2. DTγE
HVA	34.3 ± 9.0	47.0 ± 19.6	34.7 ± 35.2	42.3 ± 21.2
5-HIAA	16.9 ± 9.5	21.4 ± 7.1	19.0 ± 11.9	17.9 ± 7.7
MHPG	54	26	26	25

CSF concentrations (ng/ml) of the dopamine metabolite homovanillic acid (HVA), the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), and the noradrenalin metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in 14 schizophrenics are shown. CSF was collected at 10 a.m. via a lumbar puncture on day 9 of the peptide or placebo treatment period. Data are expressed as mean ± SD for HVA and 5-HIAA and as median for MHPG. Seven patients started with DTγE and 7 patients with placebo treatment.

Discussion

In the present controlled study, the effect of DTγE in 18 unmedicated schizophrenic patients was investigated. A slight or no antipsychotic effect was observed in six patients, a moderate reduction of psychotic symptoms in seven patients, and a marked antipsychotic effect in five patients. Three patients with a clinically significant response were treated for a second time with DTγE because of a relapse. However, in one of these patients, no antipsychotic effect occurred after the second treatment with DTγE or after subsequent treatment with clozapine. This lack of responsiveness might be related to structural changes in the cerebral substrate due to factors such as the disease process itself or biochemical disturbances. In some patients a long-lasting effect of DTγE was observed. In one of the moderately improved patients psychotic symptoms remained at the same level for 12 months after discontinuation of DTγE. Two of the five markedly improved patients functioned without further medication for more than a year at their premorbid levels. The other nine moderately or markedly improved patients relapsed at the end of DTγE treatment or within 6 months of DTγE discontinuation. Three of these patients, who had previously been partially resistant to treatment with conventional neuroleptics and who had shown moderate extrapyramidal side effects, were later treated rather successfully with low doses of sulpiride (300-600 mg/day). Their response to sulpiride might be significant because animal studies have revealed that the effects of γ-type endorphins in some respects resemble those of atypical neuroleptics, e.g., sulpiride, rather than those of classical neuroleptics (Van Ree and De Wied, 1982; Van Ree et al., 1982*a*, 1982*b*; Serra et al., 1983).

The present results confirm and extend our previous findings and support our hypothesis that DTγE has antipsychotic effects in a number of schizophrenic patients. In earlier studies (Verhoeven et al., 1979, 1981; Van Ree et al., 1981, 1982*c*), we found that patients with hebephrenic or paranoid subtypes of schizophrenia responded best to DTγE, catatonic patients responded marginally, and patients with schizoaffective psychoses, depressed type or schizophrenia, residual type did not respond. In the present study, a rather good response was also found in patients of hebephrenic and paranoid subtypes (Table 3). Moreover, two patients who were suffering from schizophrenia, residual type and schizoaffective psychosis, depressed type both failed to respond to DTγE. These results are in accord with other reports that DTγE is more effective in acute than chronic patients (Bourgeois et al., 1980; Emrich et al., 1980, 1981; Manchanda and Hirsch, 1981; Tamminga et al., 1981; Meltzer et al., 1982*a*, 1982*b*).

In addition to the relationships between DTγE response and syndromal characteristics, it was found previously that the response to γ-type endorphins is negatively influenced by a history of high dosages of neuroleptics and/or by a recent psychotic episode of prolonged duration (Van Ree et al., 1980, 1981, 1982*c*; Verhoeven et al., 1982). These findings formed part of the basis for subject selection criteria in the present study. How effective these selection criteria were in maximizing DTγE response is somewhat unclear. A higher percentage of patients responded to DTγE with a $>50\%$ decrease of symptomatology in the present study (12 of 18 patients compared with 10 of 23 in previous studies). However, because of local treatment

conditions, the selection criteria could not be very strictly applied, and it turned out that the mean previous dose of neuroleptics used by subjects in the present study was not much different from that of subjects in the earlier studies. Duration of last psychotic episode was shorter in the present study than in earlier studied samples, and moreover the present sample was enriched by a higher percentage of patients with a type of schizophrenia deemed particularly susceptible to treatment with γ-type endorphins. The present data do indicate that response to DTγE is more marked in patients with a relatively short duration of the previous psychotic episode, confirming our previous findings (Van Ree et al., 1980, 1981, in press *c*; Verhoeven et al., 1982).

Analysis of the PSE data for patients involved in the present study, as well as for the total of 30 neuroleptic-free patients we have thus far treated with DTγE in a double-blind crossover design, revealed a lower responsiveness to peptide treatment in patients presenting more symptoms belonging to the PSE syndrome of Slowness, the Catatonic and Residual syndromes. Furthermore, the response to DTγE was smaller in patients showing more pronounced negative symptoms on their baseline BPRS ratings. Similar results were obtained in our previous studies concerning treatment of schizophrenic patients with des-enkephalin-γ-endorphin (DEγE) (Verhoeven et al., 1982). These data indicate that the response to γ-type endorphins is most pronounced in patients with relatively fewer negative symptoms. Crow (1980*b*) has suggested that within the schizophrenic disorders two syndromes can be distinguished: Type I syndrome characterized by relatively more positive symptoms and greater responsiveness to neuroleptics, and Type II syndrome characterized by relatively more negative symptoms and poor long-term outcome irrespective of drug treatment (Crow et al., 1978; Johnstone et al., 1978; Crow, 1980*a*, 1980*b*). Interestingly, positive symptoms are most prominent in the hebephrenic and paranoid types of schizophrenia (Spitzer et al., 1977; American Psychiatric Association, 1980). The fact that patients most susceptible to treatment with γ-type endorphins seem to belong to the Type I syndrome links the γ-type endorphins to neuroleptics, which are likewise most effective in Type I patients.

In both the present study and a previous study (Verhoeven et al., 1981), we found that DTγE decreased the plasma PRL levels, an effect that may be related to some stimulatory influence of the peptide on the tuberoinfundibular dopaminergic system. Interestingly, the decrease of plasma PRL persisted in the placebo period of those patients assigned to DTγE during the first 10 days of the crossover study, possibly suggestive of alterations in dopamine (DA) receptor sensitivity. In animal studies, γ-type endorphins suppressed stress-induced PRL release, but dose-dependently stimulated release of PRL when basal PRL levels were low. Subchronic treatment with DEγE may affect DA receptor sensitivity because such treatment in rats resulted in an enhanced sensitivity to apomorphine with respect to its decreasing effect on PRL release (Lamberts et al., 1982). Thus, in contrast to classical and atypical neuroleptics, which elevate circulating levels of PRL, DTγE induces a small but significant decrease in plasma PRL levels.

No changes in CSF levels of HVA and MHPG were observed during DTγE treatment as compared to placebo. By contrast, classical and, to a lesser degree, atypical neuroleptics markedly increase the levels of HVA in the CSF; this effect may reflect an enhanced release and turnover of DA, probably predominantly in the

neostriatum (Van Praag and Korf, 1976; Van Praag, 1977, 1982). With respect to changes in the norepinephrine (NE) metabolites in the CSF, particularly MHPG, associated with neuroleptic treatment, the available data are limited and controversial; both decreased (Sedvall et al., 1977) and unchanged (Van Praag and Korf, 1975) levels of MHPG have been reported. Recently, concentrations of NE in CSF were found to be significantly higher in schizophrenic patients than in normal controls (Gomes et al., 1980; Lake et al., 1980), while additional results were obtained suggesting an impaired regulation of NE turnover in schizophrenia (Sternberg et al., 1982). In the present study, however, no indications were found of an influence of DTγE on nigrostriatal DA systems, central NE systems, or central serotonin systems since CSF concentrations of HVA, MHPG, and 5-HIAA were unaffected by DTγE as compared to placebo treatment. Moreover, neither plasma levels of GH nor cortisol were altered by DTγE, so it appears unlikely that DTγE interferes with central monoaminergic systems controlling the release of GH and adrenocorticotropic hormone (Lal and Martin, 1980). Nevertheless, animal experiments have demonstrated that DTγE increases DA turnover in some restricted areas of rat brain (Versteeg et al., 1979, 1982*b*) and that γ-type endorphins decrease serotonin concentrations in specific brain regions (Kurachi et al., 1982; Versteeg et al., 1982*a*). Thus, γ-type endorphins, as compared to neuroleptics, may have a selective effect on brain monoaminergic systems that is not reflected in overall changes in CSF concentrations of HVA, MHPG, and 5-HIAA or in alterations of plasma levels of GH and cortisol.

Animal experiments which showed that certain DA receptor systems in the nucleus accumbens are sensitive to γ-type endorphins suggested that these peptides are physiologically involved in the control of some, but not all dopaminergic transmission in the nucleus accumbens (Van Ree et al., 1982*a*, 1982*b*, 1982*d*). Disturbances in this control may result in a hyperactivity of DA systems sensitive to γ-type endorphins. This speculation agrees well with the hypothesis of Crow that Type I schizophrenia (characterized by positive psychotic symptoms) is associated with hyperactivity of DA systems, especially in the nucleus accumbens. Accordingly, the beneficial effects of treatment with γ-type endorphins may be the result of restoring the disturbed DA feedback systems to their physiological equilibrium (Van Ree and De Wied, 1982).

In conclusion, the present data indicate that DTγE is effective in a subgroup of schizophrenic patients characterized by the occurrence of relatively fewer negative symptoms, a relatively short duration of the last psychotic episode, and a treatment history of low doses of neuroleptic drugs. Future research should be focused on further delineating the specific subgroup of schizophrenic patients who may be successfully treated with γ-type endorphins. In addition, more reliable methods must be developed to detect schizophrenic patients with a putative disturbance in β-endorphin fragmentation resulting in a deficiency in the bioavailability of γ-type endorphins, as well as to ascertain a possible relationship between γ-type endorphins and central dopaminergic systems.

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