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Differential Effects of Des-Tyrosine-γ-Endorphin on Clinical Symptoms and EEGs in Schizophrenia

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Abstract The clinical prospects of des-tyrosine-γ-endorphin (DTγE) in schizophrenia were examined. Six male inpatients with schizophrenia were administered fixed doses of neuroleptics during this study. The EEG recording and BPRS scoring were done before DTγE administration. One mg/day of DTγE and of placebo were given intramuscularly in a double-blind, crossover design for 2 consecutive weeks, followed by 1 week of no drug treatment. The EEG recording and BPRS scoring were carried out once weekly. There were no significant differences in either the total BPRS scores or the scores of individual items between DTγE and placebo. With DTγE treatment, the power values of frontal EEGs increased slightly in the α activity during the study. The EEG values of the occipital area decreased in terms of slow wave and α activities during the study. The power of the left temporal area decreased in terms of slow wave activity in the first week but decreased in terms of fast β activity in the second and third weeks. The power of the right temporal area decreased in terms of whole bands in the first week but decreased in β activity in the second and third weeks. These results suggest that treatment with DTγE might not improve the overt symptoms of schizophrenics but might affect their EEGs in a delayed manner.

Key Words : Neuropeptide, Des-tyrosine-γ-endorphin, Schizophrenia, Clinical symptoms, Pharmaco-EEG

Introduction

Various neuropeptides were found to exist in the brain and their roles as neurotransmitters or neuromodulators in the central nervous system have been investigated. The possibility that these peptides may have efficacy in the treatment of mental illness has been suggested.[1] Terenius et al.[2] pointed out that endorphins, an opioid peptide, increased in the cerebrospinal fluid (CSF) of schizophrenic patients. This led to hypotheses such as endorphin excess, endorphin deficiency, and changes in β-endorphin fragmentation in schizophrenia.[3] β-Endorphin appears to inhibit extinction of avoidance behavior in the pole-jumping test, while γ-endorphin has an opposite effect on this behavior in that, i.e., it facilitates extinction.[4,5] Unlike the typical opiate-like action of the endorphins, their effects on conditioned avoidance behavior cannot be inhibited with the specific opiate antagonists such as naloxone and naltrexone.[4,5]

Hyperactivity of dopamine (DA) function is believed to be an important factor in the symptomatology of schizophrenia, and neuroleptics are believed to exert their antipsy-

chotic effects by blocking DA receptors.[6] Des-tyrosine-γ-endorphin (DTγE), a non-opiate-like γ-endorphin fragment, has been found to have some behavioral effects in rats consistent with a post-synaptic DA receptor blocking action.[5] It was also reported that electrophysiological and biochemical data with DTγE were consistent with a neuroleptic-like action in rats.[7,8] Based upon these results, DTγE has been used in schizophrenics. Several studies demonstrated that DTγE produced an improvement of symptoms in schizophrenic patients,[9,10] whereas others showed equivocal responses.[11,12] However, Casey et al.[13] and Tamminga et al.[14] also reported that DTγE was entirely ineffective in the treatment of schizophrenia. Thus, previous clinical studies on DTγE presented conflicting results.

The present study was undertaken to investigate the possible efficacy of DTγE as a supplement in treating schizophrenic patients by monitoring both the Brief Psychiatric Rating Scale (BPRS) and the electroencephalogram (EEG).

Materials and Methods

Subjects

The subjects in this trial were 6 male inpatients ranging in age from 22 to 41 years (mean age of 30.2 years), who were diagnosed as schizophrenic disorders by DSM-III[15] criteria. The patients continued to receive their regular maintenance doses of neuroleptics throughout the study. The backgrounds of the patients are shown in Table 1.

Drugs

One mg of DTγE or an equivalent volume of saline (placebo) was used in this study. The doses of DTγE were determined on the basis of available human data.[9]

Clinical Assessment

The BPRS[16] was used to assess symptoms, and recorded by the same 3 psychiatrists at every examination.

EEGs

Resting EEGs with eyes closed were recorded for 3 min using bipolar leads, i.e., Fz-Cz, Oz-Cz, T_3-Cz, T_4-Cz (International 10-20 Electrode System). The recording conditions were : paper speed of 1.5cm/sec, time constant of 0.1 sec, and sensitivity of 10μV/mm. The 60 Hz high-cut filter was the only one used. EEGs were recorded simultaneously on paper and on an analog tape recorder (FRC-1402N) and were analyzed for a requirement of a power spectrum by a digital computer (HR-1000) using the Fast Fourier Transform. Each 10-sec epoch was analyzed with 102.4 points/sec, which permitted the analysis of high frequencies up to 50 Hz. Time samples of 60 sec were used.

Experimental Procedure

Scoring of the BPRS, EEG recording, and

Table 1. Backgrounds of the patients

SEX	AGE	AGE at ONSET	SYMPTOMS	DSM-III	MEDICATION (mg/day)
Male	32	17	hypobulia, apathia delusion of persecution	Disorganized Type	Haloperidol 15 mg Sulpiride 300 mg
Male	27	20	deficiency of initiative hypobulia, indifference	Disorganized Type	Sulpiride 300 mg Oxypertine 60 mg
Male	22	21	deficiency of initiative hypobulia, delusion of persecution	Disorganized Type	Haloperidol 5 mg Sulpiride 600 mg Oxypertine 200 mg
Male	41	23	affective flattening hypobulia auditory hallucination	Disorganized Type	Haloperidol 12 mg Chlorpromazine 150 mg
Male	33	24	deficiency of initiative indifference	Disorganized Type	Thioridazine 60 mg Chlorpromazine 60 mg
Male	26	20	hypobulia apathia	Disorganized Type	Oxypertine 60 mg Thioridazine 30 mg

administration of DTγE and placebo were done in a double-blind, crossover design. Eight consecutive days of EEG recordings at 1300 hr and one BPRS scoring at 1000 hr were completed prior to either DTγE or placebo treatment. Subsequently, 1.0mg of DTγE or placebo was given intramuscularly once daily at 0800 hr for 2 consecutive weeks. A period of no DTγE or placebo treatment followed for the next 1 week. The BPRS scoring and EEG recording were performed 6 times at 1-week intervals after initiating DTγE or placebo treatment.

Laboratory Examinations

In order to monitor the patients' physical state, the following laboratory tests were performed before, during and after DTγE or placebo treatment : liver function tests, hematological examination, urinalysis, kidney tests, and blood pressure.

Statistical Analysis

Wilcoxon's T-test was used for statistical analysis of the BPRS scores and Student's t-test for the EEG results.

Results

BPRS Scores

In terms of both total BPRS scores as well as individual item scores, there were no significant differences between DTγE and placebo treatment at any time (Table 2). When DTγE was given (Table 2), scores for somatic concern in the third week decreased slightly, and scores for mannerisms and posturing and for uncooperativeness in the second week increased marginally as compared with the control values, respectively. When placebo was administered (Table 2), scores for mannerisms and posturing in the first and second week increased slightly as compared with the control values.

EEG Findings

In the frontal area following DTγE administration (Fig. 1), only the power values of α activity increased slightly in the first week, moderately in the second week, and slightly in the third week as compared with placebo.

In the occipital area with DTγE treatment (Fig. 2), the power values of the slow wave activity decreased in the first week, whereas those of θ, α and β bands decreased in the second week as compared with placebo. In the third week, only α activity decreased slightly.

In the left temporal area with DTγE treatment (Fig. 3), the power values of the slow

Table 2 . Effects of DTγE and placebo on BPRS

ITEMS	CONTROL	FIRST WEEK		SECOND WEEK		THIRD WEEK	
		PLACEBO	DTγE	PLACEBO	DTγE	PLACEBO	DTγE
Somatic Concern	2.67±0.42	2.17±0.40	2.00±0.68	2.83±0.40	2.50±0.34	2.50±0.43	1.83±0.40▲
Anxiety	2.33±0.49	2.83±0.75	2.17±0.83	3.17±0.83	2.67±0.84	2.50±0.96	2.67±0.61
Emotional Withdrawal	2.83±0.17	2.83±0.40	2.83±0.31	3.17±0.17	3.17±0.31	3.00±0.37	3.00±0.26
Conceptual Disorganization	1.83±0.40	2.17±0.48	2.33±0.61	2.17±0.48	2.50±0.56	2.50±0.56	2.33±0.49
Guilt Feelings	2.17±0.54	2.67±0.61	2.17±0.54	2.50±0.50	2.33±0.49	2.17±0.31	2.50±0.56
Tension	2.50±0.34	2.67±0.42	2.67±0.42	2.83±0.17	2.67±0.42	2.83±0.31	2.17±0.40
Mannerisms and Posturing	3.17±0.40	3.83±0.48▲	3.50±0.56	3.83±0.48▲	3.83±0.48▲	3.67±0.21	3.17±0.40
Grandiosity	1.50±0.34	1.33±0.33	1.17±0.17	1.17±0.17	1.17±0.17	1.00±0.00	1.67±0.42
Depressive Mood	2.50±0.43	2.00±0.45	2.00±0.63	2.33±0.61	2.33±0.49	2.17±0.40	2.00±0.52
Hostility	1.33±0.33	1.00±0.00	1.17±0.17	1.17±0.17	1.67±0.42	1.17±0.17	1.00±0.00
Suspiciousness	2.17±0.54	1.33±0.33	1.67±0.42	1.33±0.33	1.50±0.34	1.33±0.21	1.83±0.40
Hallucinatory Behavior	1.83±0.54	1.33±0.33	1.67±0.49	1.50±0.22	1.67±0.49	1.33±0.21	1.67±0.33
Motor Retardation	2.33±0.21	2.50±0.22	2.50±0.22	2.50±0.22	2.50±0.22	2.17±0.31	2.33±0.21
Uncooperativeness	1.83±0.31	3.00±0.73	2.50±0.76	2.83±0.75	3.00±0.68▲	2.67±0.61	2.00±0.63
Unusual Thought Content	2.83±0.54	2.67±0.76	2.17±0.60	2.67±0.76	2.33±0.56	2.33±0.56	2.83±0.75
Blunted Affect	3.00±0.26	3.00±0.26	3.00±0.00	3.17±0.17	3.00±0.00	3.00±0.00	2.67±0.42
Excitement	1.33±0.21	1.17±0.17	1.50±0.50	1.17±0.17	1.50±0.50	1.50±0.50	1.17±0.17
Disorientation	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00	1.00±0.00
Total	39.20±2.27	39.83±2.83	38.00±4.23	41.00±3.34	41.67±3.78	38.83±3.26	37.83±1.94

All scores of BPRS are expressed as the mean±S.E.M. Statistical analysis was performed in comparison with control values because there were no significant differences in all scores between DTγE and placebo treatment. ▲ : $P<0.10$.

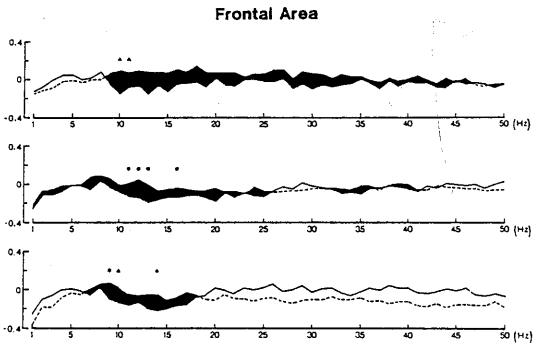

Fig. 1. Effects of DTγE and placebo on the EEG in the frontal area.

The figures are based on comparison of the EEG with DTγE and placebo treatment and the power values of the first, second and third week from the upper to lower rows, respectively. Ordinate : the values obtained by subtracting the control values from those after medication ; abscissa : frequency of EEG. The control values were calculated in accordance with a mean of EEG recorded for 7 days except for the first day. The solid line shows the values of placebo, and the dotted line the power values of DTγE. The shaded area of the figure indicates where the dotted line is above the solid line.
▲ : $P<0.10$; * : $P<0.05$; ** : $P<0.01$; *** : $P<0.001$.

wave activity decreased in the first week as compared with placebo. However, those of the fast β activity decreased slightly in the second and third weeks.

In the right temporal area with DTγE treatment (Fig. 4), the power values of the slow wave, α and β activities decreased in the first week as compared with placebo. However, those of all β activities decreased slightly in the second and third weeks.

Laboratory Findings

Laboratory findings were negative in all patients in both DTγE and placebo treatments at all times.

Discussion

The neuroleptic-like action of DTγE was based on the similarities between the effects of this peptide and of haloperidol on the

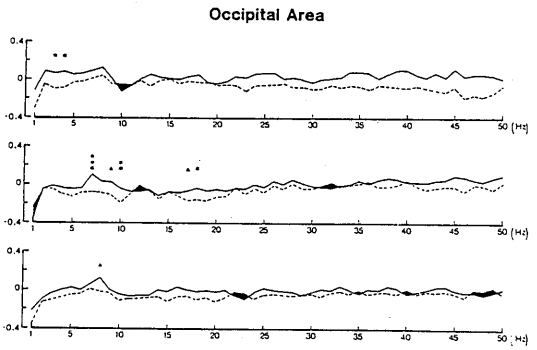

Fig. 2. Effects of DTγE and placebo on the EEG in the occipital area.
The details are in the legend for Fig. 1.

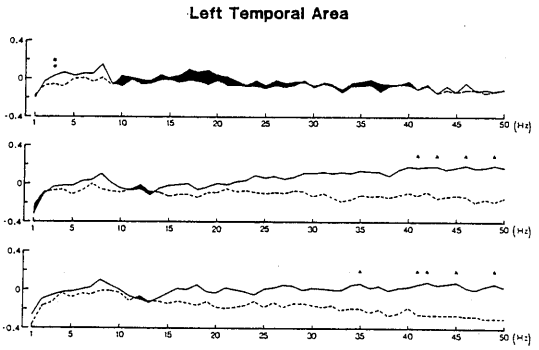

Fig. 3. Effects of DTγE and placebo on the EEG in the left temporal area.
The details are in the legend for Fig. 1.

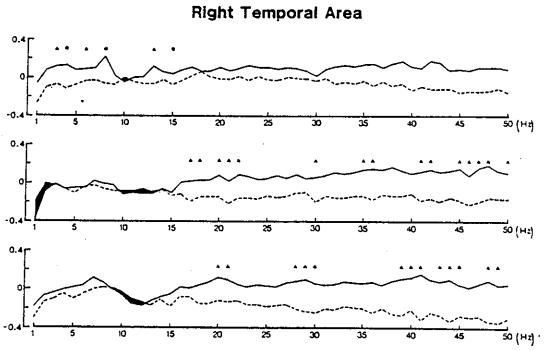

Fig. 4. Effects of DTγE and placebo on the EEG in the right temporal area.
The details are in the legend for Fig. 1.

extinction of pole jumping behavior and on passive avoidance behavior and because both compounds induced a grasping response.[5,17] These behavioral effects suggested that DTγE possessed a postsynaptic DA receptor blocking action.[5] Furthermore, DTγE antagonized the hypoactivity induced by low doses of apomorphine, but had no effect on the stereotypy elicited by high doses of apomorphine or by amphetamine.[18] These findings also suggested that DTγE acted as an antagonist at presynaptic DA receptors. However, several studies reporting biochemical evidence are inconsistent with a DA receptor antagonist action.[19,20] It was also reported that DTγE may influence presynaptic DA synthesis and release.[21,22,23] In some treatment trials, DTγE showed a therapeutic effect in schizophrenia,[9,10] but negative reports regarding an improvement effect in schizophrenia have also been published.[13,14]

In the present study, DTγE failed to exert a decrease in both total BPRS scores and scores on individual items at all times. Only scores for somatic concern in the third week slightly decreased as compared with the control values. Van Ree et al.[3] reported that DTγE was more effective in schizophrenic patients characterized by a short duration of the last psychotic episode, (more effective in acute schizophrenia than in chronic schizophrenia), a treatment history of no medications and with low doses of neuroleptic drugs, as well as in patients suffering from the hebephrenic type of schizophrenia. Verhoeven et al.[24] also pointed out that a beneficial effect of DTγE could be expected in patients who had the occurrence of fewer negative symptoms in addition to the suggestions of Van Ree et al.[3] The majority of patients in this study had both an acute and chronic course, a treatment history with high doses of neuroleptics, and primarily negative symptoms. Thus, positive results would not be expected with DTγE treatment in these patients. Volavka et al.[25] reported that the improvement of schizophrenic symptoms by administration of DTγE was limited to the only first 3 or 4 days of the treatment. This suggests that the action of DTγE used in the present study had already disappeared at the time of the BPRS scoring period 1 week following DTγE administration. Another possibility is that DTγE may influence presynaptic DA synthesis and release as mentioned by Schoemaker and Nickolson,[21] Nickolson and Berendsen[22] and Davis et al.[23] Therefore, scores for mannerisms and posturing and for uncooperativeness in the second week might be only slightly impaired as compared with the control.

Itil et al.[26] reported that drug-refractory schizophrenic patients showed more potent negative symptoms than positive symptoms, as well as some fast β activity and much slow α and slow wave activities in the EEG in the right occipital area. Furthermore, patients who responded to treatment showed strong positive symptoms, much fast β activity, and slight α activity. Itil[27] also noted that an increase of α activity and a decrease of fast β activity were observed after amelioration of positive symptoms. The relationship between no improvement of clinical symptoms by DTγE administration and the decrease of α activity and no change of fast β activity in the occipital area was parallel in this study, however, the occipital slow wave activity also decreased in the first and second weeks. The α activity in the frontal area increased slightly throughout the study in spite of ineffectiveness in the treatment of symptoms. From our previous pharmaco-EEG studies on some neuropeptides,[28,29] it has been suggested that EEGs in the frontal area reflected primarily changes in the schizophrenic symptoms. Volavka et al.[25] also found a high rate of formation and of degradation by testing the metabolism of DTγE in the patients' plasma, but the metabolic rates were not related to clinical symptoms. Thus, DTγE may possess differential effects on clinical symptoms and biological indices in schizophrenia. That no improvement in clinical symptoms was seen with DTγE is also inconsistent with the observed changes in both temporal EEGs such as a decrease in slow wave activity in the first week and a decrease in fast β activity in the second and third weeks. However, the present data showed that changes in the right temporal region were more pronounced than

those in the left temporal region. There are many reports concerning the functional laterality of the cerebral hemispheres in schizophrenia, and it has been suggested that the left hemisphere shows a functional disturbance or hyperactivity in this disorder.[30] Therefore, the findings in temporal areas may indicate a lack of flexibility in the left hemisphere due to either a functional disturbance or to hyperactivity in this region. Furthermore, changes in the EEGs of all areas continued even into the third week without DTγE administration. This may indicate that DTγE has a long-lasting central effect. This interpretation is also supported by the results of scores of somatic concern from the BPRS.

Laboratory findings did not reveal any abnormalities. Therefore, it may be assumed that DTγE is a comparatively safe neuropeptide with minimal side effects. Although a more definitive study without other medication and with a larger population will be necessary, the present study suggests that treatment with DTγE might not improve the overt symptoms of schizophrenics but might affect their EEGs in a delayed (2 to 3 weeks after administration) fashion.

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