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Clinical Investigations for Emotional Effects of Neuropeptide Hormones

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EHRENSING, R. H. AND A. J. KASTIN. *Clinical investigations for emotional effects of neuropeptide hormones.* PHARMAC. BIOCHEM. BEHAV. 5: SUPPL. 1, 89–93, 1976. – After the demonstration that hypothalamic peptides can have a direct effect on the central nervous system, a series of studies was initiated to investigate the hypothesis that hypothalamic peptides could have an effect on emotions and affect. TRH was administered to 6 patients with endogenous depressions in a double-blind, cross-over design with transient improvement in the mental depression of 4 of the 6 patients. In a second study involving 8 seriously depressed patients given 1000 μg of TRH for 10 days, no significant antidepressant effect of TRH was observed. In a pilot, double-blind study of 18 women with endogenous depressions, the group receiving MIF-1 60 mg per day in a single daily dose for 6 days responded better than the placebo group, which in turn responded better than the group receiving MIF-1 150 mg per day. In a second, double-blind study testing MIF-1 in endogenous depressions, 5 patients met the criteria for substantial improvement out of a total of 8 receiving MIF-1 75 mg per day. In contrast, only one patient met these criteria in each of the remaining 2 groups, consisting of 10 patients receiving MIF-1 750 mg per day and 5 patients receiving placebo. Finally, 6 men complaining of decreased libido and/or potency were given intravenous injections of LHRH 700 μg or saline once daily for 3 consecutive days per week in a double-blind, cross-over design. In addition, 3 men were given much higher doses of LHRH in a single-blinded study. No substantial effect on libido or sexual performance was observed.

TRH MIF-1 LHRH Mental Depression Libido Sexual Impotence Hypothalamic peptides Antidepressant therapy

AFTER the demonstration in animals that hypothalamic peptides can have a direct effect on the central nervous system not mediated by the pituitary [15,19], we began to investigate the possible effects of hypothalamic hormones on emotion and affect in man. We were initially interested in testing the effect on mental depression of melanocyte-stimulating-hormone release inhibiting factor (MIF-1, prolyl-leucyl-glycinamide), since MIF in animal studies had shown itself more effective than the tricyclic antidepressants in the dopa response potentiation test [19] and reversed the sedative effects of deserpidine in mice and monkeys [20], 2 animal models used to screen for potential antidepressant agents. Since thyrotropin releasing hormone (TRH, pyroglutamy-histidyl-proline amide) was also active in the dopa potentiation test [21] and MIF-1 was not readily available at the time for clinical testing, we proceeded to test the effect of TRH in mental depression first, followed by clinical studies with MIF-1. We were encouraged to report our preliminary results with TRH in depression by the positive report of Prange and Wilson [22]. Finally, the reports that luteinizing-hormone-releasing-hormone (LHRH) enhanced sexual interest and behavior in animals [17,18] as well as had a similar effect in hypogonadal men [16,23], led us to investigate the effects of LHRH on decreased libido and psychogenic impotency in man.

We will report the results of 5 of our research studies into the effects of hypothalamic peptides on depressed affect and libido and discuss the hypothesis that hypothalamic peptides have effects on emotions and affect.

METHOD

Study A TRH in Mental Depression - 1

Six patients with endogenous depressions were administered 500 μg of TRH or saline intravenously for 2 consecutive 3 day periods using a double-blind, cross-over design. Patients were evaluated with the Hamilton Rating Scale for depression, the Zung Self Rating Scale for depression, a self assessment global scale, and an examiners global rating. The examining psychiatrist, on the basis of the patient's self rating as well as his evaluations, designated the 3 day period during which the greater clinical improvement occurred [14].

Study B – TRH in Mental Depression - 2

Eight seriously depressed patients, 6 women and 2 men, 7 with endogenous depressions and 1 with a psychotic depressive reaction, were given a single, rapid, intravenous injection of 1000 μg of TRH or saline daily for 3 days (Days 1–3) in a double-blind design. For the next 7 days (Days 4–10) all patients received 1000 μg of TRH intravenously daily in a single-blind design. Patients were evaluated with the Hamilton Rating Scale for depression on Days 1, 4, 7, 11 and daily before their injections with a Global Severity of Illness Scale (Range 0–6). The patients rated themselves daily with a Zung Self Rating Scale for Depression and 3 times a day using a line self rating scale for depression. A patient was judged to be substantially improved during the first 3 days or during the following 7 day period if 3 of the following 4 criteria were satisfied: (a) if 50 percent or greater reduction in the Hamilton Score; (b) a reduction of the Zung Self Rating Score into the normal range of 45 or less; (c) a reduction in the Global Severity of Illness Scale to less than three; and (d) a reduction of 50 percent and greater in the amount of depression indicated by the Line Self Rating Scale [11].

Study C MIF-1 in Mental Depression - 1

Eighteen women, 35 to 61 years old, with unipolar mental depressions were tested for 9 days. The first 3 days of the investigation, (Days 1–3) each patient received as a single, morning, oral dose, 6 capsules containing a placebo. For the next 6 days (Days 4–9) all the women continued to receive the same number of identical appearing capsules each morning: one-third (6) of the patients continued to receive placebo, 6 patients received 60 mg of MIF-1 daily and 6 patients received 150 mg MIF-1 daily. The initial lead-in period was single-blinded with the treatment period double-blinded. The patients were evaluated by the Hamilton Rating Scale for depression every 3 days and by a Global Severity of Illness rating daily. The patients rated themselves by means of the Zung Rating Scale for Depression, A NIMH symptom self evaluation form every 3 days and by a line self-rating for depression 3 times daily.

Criteria for substantial improvement were: (1) a 50 percent or greater reduction in the Hamilton score; (2) a reduction on the Zung score into the normal range of 45 or less; (3) a 50 percent or greater reduction in the line self-rating; (4) a reduction in the NIMH symptom score to 60 or below; (5) a decrease in the Global Severity of Illness rating to below 3. If 4 out of the 5 criteria were met for either the placebo period or the drug trial period, the patient was judged to be substantially improved during that period [8].

Study D MIF-1 in Mental Depression - 2

Twenty-three patients, 18 women and 5 men, ages 23–61 with endogenous depressions of both the unipolar and bipolar type, off antidepressant medicaiton for 2 weeks, were included in a double-blind study of 5 treatment regimens: Placebo, MIF-1 25 mg t.i.d., MIF-1 75 mg in a single dose in the morning, MIF-1 250 mg t.i.d. and MIF-1 750 mg in a single a.m. dose. All patients received 3 daily doses of the same number of identically appearing capsules for a total of 5 days (Days 1–5). Patients were evaluated with the Hamilton Rating Scale and a NIHM 35 Symptom Self Rating Scale on Days 1, 3 and 6; by a Zung Self Rating Scale for Depression on Days 1 and 6; by the examiner's Global Rating Scale daily and a Line Self Rating Scale 3 times a day. The same criteria for substantial improvement as used in Study C were employed.

Study E LHRH in Decreased Human Libido

Six men complaining of decreased libido or impotency for which no organic basis could be discovered were given intravenous injections once daily for 3 consecutive days per week at the beginning of 2 consecutive weeks. The patients received either LHRH 700 μg or saline in a double-blind, cross-over design. One woman also complaining of decreased libido took part in the study. Patients reported their sex drive and sexual performance by means of daily and weekly questionnaires and rated which of the 2 weeks, if any, was superior in terms of increased libido. In addition 3 men were given LHRH 1250-3000 μg per dose in three consecutive intravenous doses per week from 1 to 3 weeks in a single-blinded study using the same questionnaires.

RESULTS

Study A

One patient was found to be hypothyroid on the basis of her T-3, T-4 and TSH response to TRH. Of the 5 remaining euthyroid patients, all 5 were assessed as showing more clinical improvement during the 3 day period they received TRH. Four patients experienced marked improvement at some time during this 3 day period and the remaining patient experienced mild improvement. The first sign of improvement occurred from 1 to 6 hr after the first injection for 4 patients to several hours after the third injection for the remaining patient. The duration of improvement lasted from 3 hr to three days. However, 3 out of the 5 patients, 3 out of the 4 with marked improvement, received TRH for the first period of 3 days, increasing the chances that an initial placebo effect and an order of treatment effect would appear to be caused by TRH. The sixth, hypothyroid patient was also assessed as showing moderate clinical improvement during the time that she received TRH. It was our opinion that no definite conclusion could be reached from this study concerning the use of TRH as an antidepressant.

Study B

Saline was superior to TRH during the initial 3 day double-blind period, with 3 of the 4 patients receiving saline and none of the 4 patients receiving TRH showing substantial improvement (Table 1). During the 7 days all of the patients received TRH (Days 4–10), those patients who had improved on saline maintained their improvement. Only one patient who had not improved went on to show substantial improvement while on TRH. We concluded there seemed little evidence from this study to suggest TRH is a clinically useful antidepressant.

Study C

Four patients showed substantial improvement by the end of the initial 3 day placebo period and continued to improve regardless of what they received for the remaining 6 days (2 patients on placebo, 1 patient each receiving 60 mg or 150 mg daily of MIF-1). Of the patients not substantially improved by Day 4, 4 out of the 5 patients

TABLE 1

LACK OF SUBSTANTIAL IMPROVEMENT IN MENTAL DEPRESSION WITH TRH (1000 μg I.V. DAILY FOR 7 -10 DAYS)

	Patient No.	Sex	Age	Diagnosis	Substantial Improvement Days 1 - 3	Days 4 - 10
TRH Days 1 - 10	1	F	27	Unipolar	No	No
	3	F	52	IM	No	No
	5	M	35	Bipolar	No	Yes
	8	F	42	Unipolar	No	No
Saline Days 1 - 3	2	F	48	PDR	Yes	Yes
	4	F	33	Unipolar	Yes	Yes
TRH Days 4 - 10	6	F	49	Unipolar	Yes	Yes
	7	M	47	Unipolar	No	No

IM = Involutional melancholia
PDR = Psychotic depressive reaction

receiving 60 mg of MIF-1 showed substantial improvement by Day 10, with most improvement occurring after 24 hr and before 48 hr following the first dose of MIF-1. Two of the 4 patients continuing to receive placebo improved substantially by Day 10. The group given 150 mg of MIF-1 each day had the poorest overall response with only 2 of the 5 patients improving substantially. Figure 1 demonstrates the different responses of the 3 groups by the mean decrease in the Hamilton score for each group from the morning of Day 4, the beginning of the treatment period. The only test showing any statistically significant difference between the groups was the Line Self Rating (Fig. 2). The patients receiving 60 mg MIF-1 showed more improvement ($p<0.05$, Duncan Multiple Range Test) than the group receiving the placebo on Days 5 and 6 and than the group receiving the 150 mg dose on Days 6, 7 and 9.

Improvement was sustained for a minimum of one month to indefinitely for many patients. One patient began to relapse after one month and after 3 months she was rehospitalized and given a repeat trial of 60 mg of MIF-1 with the examiner remaining blind for both trials. The initial placebo period was omitted and within 3 days she again responded with substantial improvement to the second trial of MIF-1.

Study D

Again the lower doses of MIF-1 were associated with more improvement in depression compared to placebo. Also the higher doses of MIF-1 were again associated with less improvement than that seen with placebo. Listed in order of improvement the groups are as follows: MIF-1 75 mg q. a.m. two patients met the criteria for substantial improvement out of a total of 3 patients in the group; MIF-1 25 mg t.i.d. 3 patients substantially improved out of a total of 5 patients; MIF-1 250 mg t.i.d. 1 patient substantially improved out of a total of 6 patients; and MIF-1 750 mg q. a.m. no patients substantially improved out of a total of 4 patients. Combining the 4 treatment groups into high and low total daily dose groups, the MIF-1 75 mg per day group had 5 patients showing substantial improvement out of a total of 8; the MIF-1 750 mg per day had 1 patient showing substantial improvement out of a total of 10 patients. Except in the case of 1 patient in the MIF-1 75 mg per day dose, improvement was substained for at least one week and usually longer.

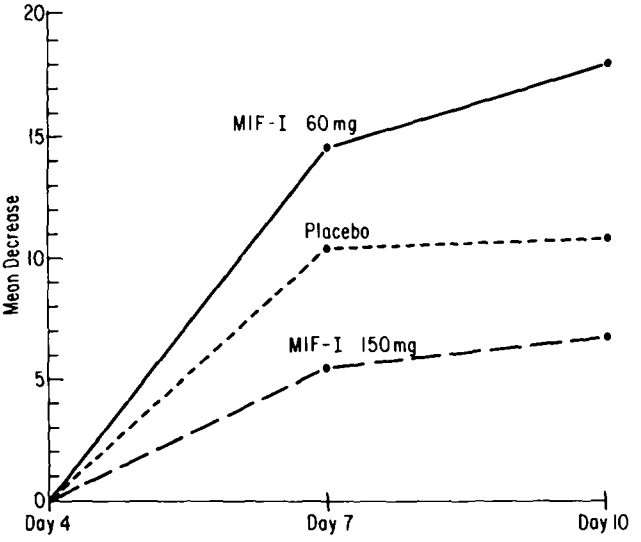

FIG. 1. Mean decrease in Hamilton Rating Scale for Depression with MIF-1 60 mg, MIF-1 150 mg, and placebo.

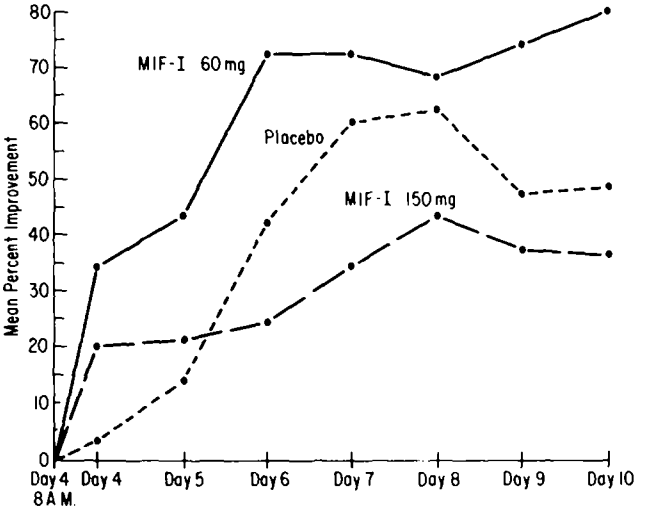

FIG. 2. Mean percent improvemnet in Line Self Rating Scale for Depression with MIF-1 60 mg, MIF-1 150 mg and placebo.

Study E

This study was remarkable by the absence of a placebo effect. Very little effect was also seen from LHRH with only one man patient in the double-blind study reporting any clear increase in libido and potency during the time he received LHRH. The 1 woman in the study reported no improvement in her libido and rated the week she received saline as slightly better than the week she received LHRH. The men who received the higher doses of LHRH reported no clear improvement in their sexual ability or interest.

DISCUSSION

Despite early optimistic reports, TRH has not been

found to be a generally effective antidepressant agent in numerous studies employing various doses and routes of administration and diagnostic categories of depression. In our review of the literature [9], we found 4 positive single-blinded studies involving a total of 21 patients suggesting a possible antidepressant effect of TRH. There were 2 positive double-blind studies involving a total of 15 patients. In contrast, there were 8 negative double-blind studies employing both the intravenous and higher dose oral routes of administration of TRH to a total of 94 depressed patients with both endogenous and reactive depressions. In addition there were 2 negative single-blind studies involving a total of 35 patients. We concluded that there is little evidence to consider TRH a clinically effective antidepressant, although there remains a distinct possibility that there are occasional patients with mental depression who do respond to TRH. If indeed these patients do have a specific response to TRH, they at present are not a readily identifiable minority and respond to TRH much like an idiosyncratic side effect.

Despite an initial report of improvement in four chronic schizophrenic patients [24] as reflected by a decrease in their rate of hallucinations and overall score on the Brief Psychiatric Rating Scale after intravenous TRH, double-blind controlled studies with TRH have failed to detect any clinical effectiveness TRH in schizophrenia [5,6].

The picture is not as clear with MIF-1 in mental depression. Our two studies suggest that MIF-1 may have an antidepressant effect which can be clinically useful and which in some patients is assocated with extended improvement. In our studies we have seen a greater antidepressant effect associated with the low oral dose of MIF-1 than with the higher dose, a finding somewhat like that observed in Parkinson's disease [2,3]. In lower doses, oral MIF-1 produces an EEG profile similar to amitriptyline, while in higher doses the profile resembles that seen with amphetamines and other psychostimulants [13]. In our study of MIF-1 in tardive dyskinesia [10], we saw more improvement in the dyskinesia with the lower oral dose. In that same study, we found no substantial clinical improvement in the psychiatric condition of the 13 chronically institutionalized patients with schizophrenia and chronic organic brain syndromes. These clinical studies, as well as the potentiation of dopa in animals, suggest that MIF-1 acts by affecting CNS dopamine tracts. MIF-1 is reported to potentiate the motility effect of the dopamine agonist apomorphine on rats rendered akinetic by a 6-hydroxydopamine hypothalamic lesion, pointing to the postsynaptic dopamine receptor as the possible site of action of MIF [2]. However, the role of dopamine pathways in mental depression is not clear.

There is the possibility that MIF-1 may not be absorbed well orally or is degraded in the gastrointestional tract or altered in its passage throught the liver. More recent reports indicate intravenous doses of MIF, 200 mg, plus oral levodopa are more effective in Parkinson's disease with an improvement in the patients' mood [1,2]. Fischer *et al.* [12] reported improvement in Parkinson patients' mood with MIF-1, 30 mg a day intravenously for 2 weeks.

While Doering *et al.* [7] reported an increase in sexual interest in normal volunteers after injections of LHRH at a dose lower than that we employed, and despite clinical studies reporting an increase in libido in hypogonadal men receiving LHRH [16,23], to date there have been no well controlled studies clearly demonstrating a clinically useful effect of LHRH to increase sexual interest and performance. A double-blind, placebo controlled study by Benkert *et al.* [4] suggests that LHRH must be first administered several weeks but that an increase in sexual potency is only seen after LHRH has been discontinued for 4–6 weeks. We are currently undertaking a study using higher doses of LHRH over a much longer period of time to fully assess its potential for increasing male sexual potency and libido where both are pathologically depressed.

In summary, clinically useful effects of hypothalamic peptides on human affect and emotion remain to be substantiated. TRH does not appear to have any general clinical usefulness as an antidepressant and the possible effectiveness of MIF-1 as an anti-depressant remains encouraging but far from proven. LHRH may have some role in substantially increasing human sexual potency and libido but investigations have not yet adequately supported this hypothesis by rigorously controlled clinical studies.

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