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# An Analog of MSH/ACTH 4-9 Enhances Interpersonal and Environmental Awareness in Mentally Retarded Adults

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SANDMAN, C. A., B. B. WALKER AND C. A. LAWTON. *An analog of MSH/ACTH 4-9 enhances interpersonal and environmental awareness in mentally retarded adults.* PEPTIDES 1(1) 109-114, 1980.—In a double blind procedure, four doses (0, 5, 10 and 20 mg) of an orally active analog of ACTH/MSH 4-9 was administered to mentally retarded adults. Changes in behavior and in productivity were evaluated as subjects performed their job in a sheltered workshop. During the first week productivity suffered while behavior related to communication and sociability increased in clients receiving the peptide analog. During the second week, clients given the peptide were more productive and attentive to environmental events while differences in sociability stabilized. Five and 10 mg enhanced productivity of tasks requiring precision and concentration whereas 20 mg depressed performance of all tasks. Regression equations indicated that different doses of the peptide generated unique relationships between behavior and productivity with self-stimulation characterizing the clients given the peptide. The use of the peptide analog of ACTH/MSH as a potential treatment with the mentally retarded is encouraged by these findings.

ACTH/MSH 4-9 analog      Awareness enhancement      Mental retardation

THE view of brain-behavior relationships has undergone major revisions in the last decade. The traditional view of the brain which ascribes function to specific structures has been challenged by a view which emphasizes dynamic process in the brain. Paramount among the sources of challenge is the work with polypeptide hormones. These substances are found in great quantities in the brain (and not just in the pituitary as was once thought) and appear to have discrete relationships with behavior. Further, they are in constant flux and replacement paralleling the incredible variability and unpredictability of behavior.

Among the most widely studied polypeptide hormones are adrenocorticotrophic hormone (ACTH) and melanocyte-stimulating hormone (MSH). These two molecules share a behaviorally active heptapeptide sequence, Met-Glu-His-Phe-Arg-Try-Gly (ACTH/MSH 4-10). Rats injected with

ACTH/MSH 4-10 evidence delayed extinction of avoidance [3] and appetitive responses [11]. While these data have been interpreted as indicating that ACTH/MSH 4-10 improves memory [3] or influences the motivational state of the organism [4], other data have suggested that the heptapeptide improves selective attention. For example, rats treated with ACTH 4-10 or MSH evidence more rapid reversal of a black-white discrimination problem than saline treated controls [7,12].

Research with normal human subjects has supported the speculation that attentional functioning is enhanced by ACTH/MSH 4-10 [6, 8, 9, 15]. Subjects given the peptide reproduced detailed geometric forms, discriminated relevant cues in a concept formation task, showed augmented physiological orienting responses during presentation of novel stimuli and displayed attentional improvement without

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enhanced memory in the Sternberg Item Recognition Task. This speculation was tested further by examining the influence of MSH/ACTH 4-10 in mentally retarded subjects who suffered from attentional and stimulus processing deficits. Injection with the peptide enhanced these subjects' ability to notice and detect changes in their environment and to attend selectively to relevant dimensions of stimuli [10]. Recently these findings were replicated using an orally active analog of MSH/ACTH 4-9 (H-Met (O<sub>2</sub>)-Glu-His-Phe-D-Lys-Phe-OH) [14]. The present study is the first to describe the influence of the MSH/ACTH analog in a natural workshop environment where facilitation of selective attention may have adaptive significance. Further the workshop environment provided the first opportunity to observe the influence of peptides on interpersonal behavior.

The environment we investigated was a sheltered workshop for mentally retarded adults. Clients in the workshop were paid a wage based on their productivity. We examined the task of shaping electrical resistors so they fit a mold. The task had several steps (turning the leads, bending, cutting and inspecting) but the clients were assigned a single step for the day. (Conversion factors supplied by the workshop equated the tasks for productivity.) Each step was monotonous and repetitious and productivity was disrupted by a lack of concentration, uncoordination or other extraneous activities of the client. Thus it appeared possible that the ACTH 4-9 analog might influence productivity as well as the clients' related behavior.

#### METHOD

##### Subjects

Only adult clients (ages 18-31) who were free of seizures and not receiving major medication were considered for inclusion in the study. Twenty-two clients (15 men and 7 women) volunteered to participate. We required that the subjects and their guardians understood the procedures and gave their signed consent. The clients who participated in the study were not segregated from the clients who did not participate. Clients were tested only in the morning between 0800 and 1100 but arrived at variable times and worked variable lengths of time. However, all clients worked at least 2 hours each morning and ate breakfast before receiving their capsules.

##### Procedure

The procedures for measuring productivity, observing behavior and administering the peptide analog were divided into several segments. During the first week (pilot week) the experimenters performed all of the measurements without administering the capsules. The purpose of this phase was to establish the reliability of the observational procedures and to accommodate the clients to the presence of the experimenters. The interrater reliability of the behavior ranged between .74 and .96 among the experimenters.

During the second week a placebo capsule (0 mg) was administered to each subject immediately before beginning work. The purpose of this phase was to familiarize the clients with the "medication" procedure in order to eliminate expectancy and novelty effects. Only data collected on days 3-5 were used during this phase since the first two days were disrupted significantly by the procedures. During the following 2 weeks (3 and 4) the subjects were administered 1 of 4 doses (0, 5, 10 and 20 mg) of the ACTH 4-9 analog. In a double-blind procedure, each subject received 2 different

TABLE 1  
BEHAVIORAL CATEGORIES USED TO ASSESS THE INFLUENCE OF  
MSH/ACTH 4-9 ANALOG

1. Looking away while working.
2. Looking away without working.
3. Doing nothing.
4. Concentration on work.
5. Uncoordination.
6. Talking to oneself.
7. Talking to worker.
8. Client talks to supervisor.
9. Supervisor talks to client.
10. Listening.
11. Restless movement.
12. Walking away from work area.
13. Stretching and yawning.
14. Gestures (hand, body, head).
15. Positive Gestures.
16. Negative Gestures.
17. Being touched by others.
18. Touching others.
19. Self-stimulation.

doses, one dose every day for 5 consecutive days during week 3 and a different dose every day for 5 consecutive days during week 4.

The workshop was a very large open room containing 14 workbenches. Four to 10 clients occupied each bench. No effort was made to create a controlled environment, consequently the normal amount of noise and movement was tolerated. Every 30 minutes the number of resistors completed by each client was counted without interfering with the work of the clients. One-minute samples of behavior were collected during each 15 minute interval for 2 hours after administration of the capsule. The observation involved tallying the frequency of behaviors which were *initiated* by each client during the sampling period. The behavioral categories are listed in Table 1. Several of the categories were included based upon previous research and others were included because preliminary observation of clients (week 1) indicated that these behaviors were highly probable.

#### RESULTS

In order to minimize the exaggerated individual differences and permit meaningful statistical analysis, covariance procedures were employed. The number of resistors completed and the frequency of behaviors during placebo treatment (week 2) served as the covariate. A complex factorial design included analysis of dose (0, 5, 10, and 20 mg), of weeks 3 and 4, of five days and four half hour intervals. In addition, multiple stepwise regression equations were computed to predict productivity from the behavior of the clients and discriminant function analysis was employed to determine group membership for clients receiving various doses of the peptide.

##### Productivity

As illustrated in Fig. 1, significantly different patterns of work performance were associated with the doses of the peptide analog,  $F(1,18)=3.86, p<0.03$ . The values presented in Fig. 1 for week 3 indicate that all three doses of the peptide

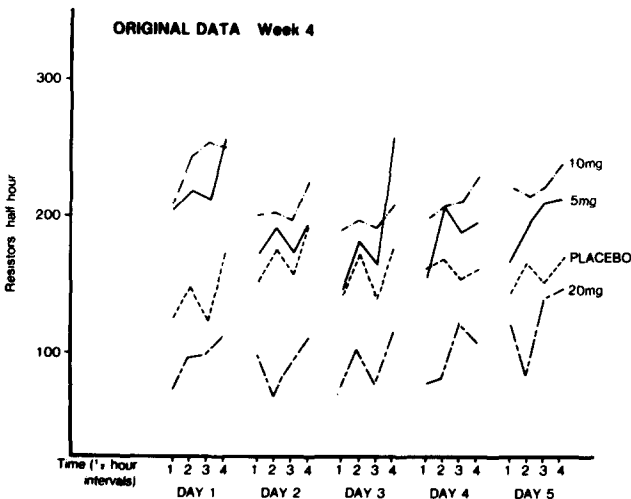
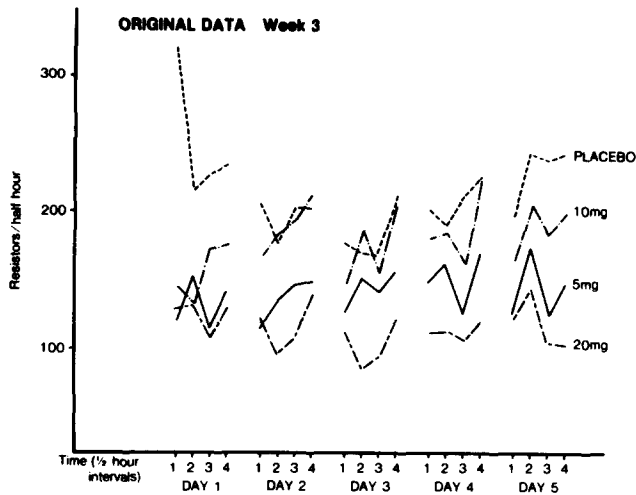


FIG. 1. Resistors produced during weeks 3 and 4 following treatment with 0, 5, 10 or 20 mg of an analog of MSH/ACTH 4-9. During week 3 treatment with placebo resulted in superior productivity and 20 mg in depressed productivity. During week 4, 5 and 10 mg resulted in superior performance.

analog depressed productivity with the 20 mg dose exerting the greatest effect. Further the apparent bitonic influence of 5 and 10 mg of the peptide over time and days coupled with the U-shaped function for subjects given the placebo resulted in a highly significant 3-way interaction,  $F(36,228)=2.02, p<0.01$ .

During the fourth week the initial trend was reversed and the clients treated with the peptide completed a greater number of resistors than subjects given the placebo (Fig. 1). The different influence of the MSH/ACTH 4-9 analog on productivity during weeks 3 and 4 was reflected in a significant interaction,  $F(36,444)=1.57, p<0.02$ .

Although conversion factors were used to equate the tasks, qualitative differences among the tasks were apparent. The first step of the process involved making turns in the wire leads of the resistors. The second step required smaller, more discrete bends in the leads. The third step was cutting the leads to a prescribed length. The fourth step involved inspecting the resistors and making decisions as to whether

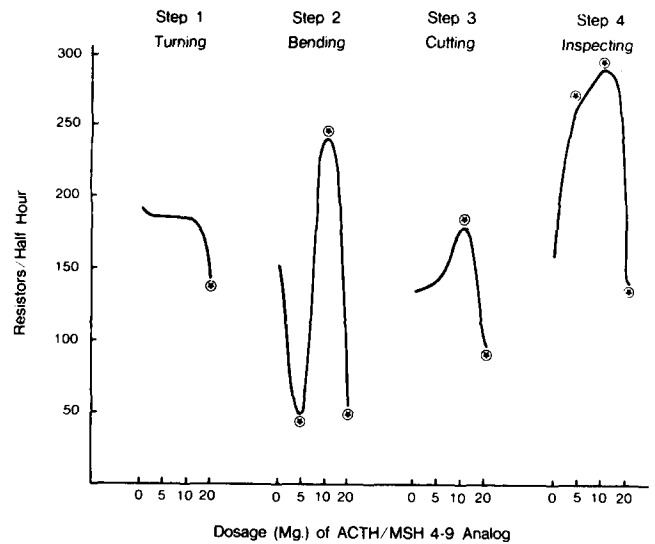


FIG. 2. The influence of dosage of the ACTH/MSH 4-9 analog on various steps of the task of producing resistors. The stars signify a significant difference from the 0 mg dose.

they met the quality criteria established by the workshop. Clearly the third and fourth steps involved the greatest precision. Separate correlated *t*-tests were computed for each task comparing each dose of the peptide with placebo treatment collapsed across weeks. The results are illustrated in Fig. 2. Ten milligrams of the peptide enhanced all but the first step of process. Conversely 20 mg depressed performance of each step. The influence of 5 mg was mixed, enhancing performance of tasks requiring precision (step 4, inspection) and impeding a task involving less precision and more rote activity (bending, step 2). These data offer support for the contention that 10 mg of the peptide enhances a spectrum of behaviors, 20 mg depresses performance regardless of the task and the smaller dose (5 mg) exerts discrete effects, enhancing tasks requiring concentration and depressing performance of less demanding tasks.

*Behavior*

Different profiles of behavior also were related to the four doses of the peptide analog. During the third week (first week of treatment), clients given the peptide, especially 10 mg, talked with fellow workers significantly more,  $F(3,18)=5.23, p<0.01$ , than clients given the placebo. The use of gestures as forms of communication increased significantly,  $F(9,57)=2.02, p<0.05$ , within days, each day, for subjects given 10 or 20 mg of MSH/ACTH 4-9. This behavior also was virtually absent for subjects given the placebo. The greater occurrence of positive facial expressions in subjects given the peptide, especially 10 mg, was marginally significant,  $F(3,18)=2.61, p<0.08$ . Self-stimulation (touching self, lip smacking, etc.) was observed significantly more often in clients given the MSH/ACTH 4-9 analog. From Fig. 3 it is apparent that this behavior increased linearly over days for clients given 10 and 20 mg while decreasing over days in clients given 5 mg. However, the 5 mg dose resulted in much higher initial values and by the end of the week (days 4 and 5) all clients receiving the peptide were at about equal rates. During placebo treatment little self stimulation was observed. This complex interaction was statistically reliable,  $F(12,76)=2.02, p<0.02$ .

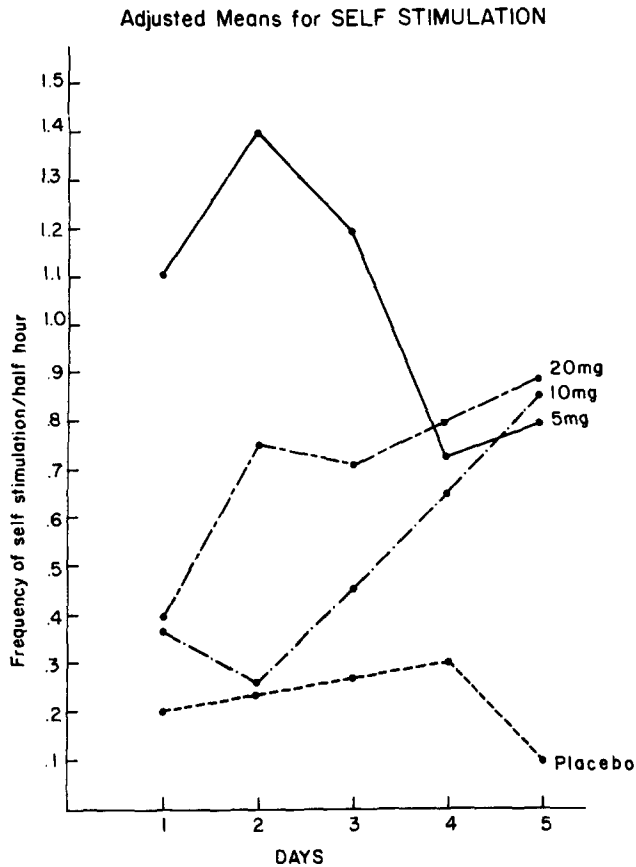


FIG. 3. The frequency of self-stimulation during the third week as a function of dose of the peptide analog and days of treatment. (The values are adjusted for initial values by covariance techniques.)

During the fourth week, clients given the peptide analog concentrated on their work more than clients given placebo,  $F(3,17)=2.88, p<0.06$ . The effect was due exclusively to clients given 10 mg. More restless movement was observed among clients given the peptide with a significant increase in subjects receiving 10 mg and 20 mg. Figure 4 illustrates several of the differences described and depicts the changes which occurred between week 3 and 4. The differences between weeks for placebo treatment may be partially attributed to the fact that clients receiving placebo week 4 had received 5 days of the peptide week 3. It is noteworthy that the differences in self-stimulation observed week 3 disappear during week 4 only because of the increase in the placebo group. Another dramatic change is the marked increase in work related behavior during week 4 compared to elevated social behavior during week 3 for clients given 10 mg of the peptide analog.

*Relationship Between Productivity and Behavior*

Since productivity may be related to the behavior of the clients, stepwise multiple regression equations were computed with the number of resistors as the criterion variable and the frequency of behavior as the predictor variables. (The regression coefficients were generated using subjects $\times$ observation. The equations reflect conservative within subject variation.) The results, summarized in Table

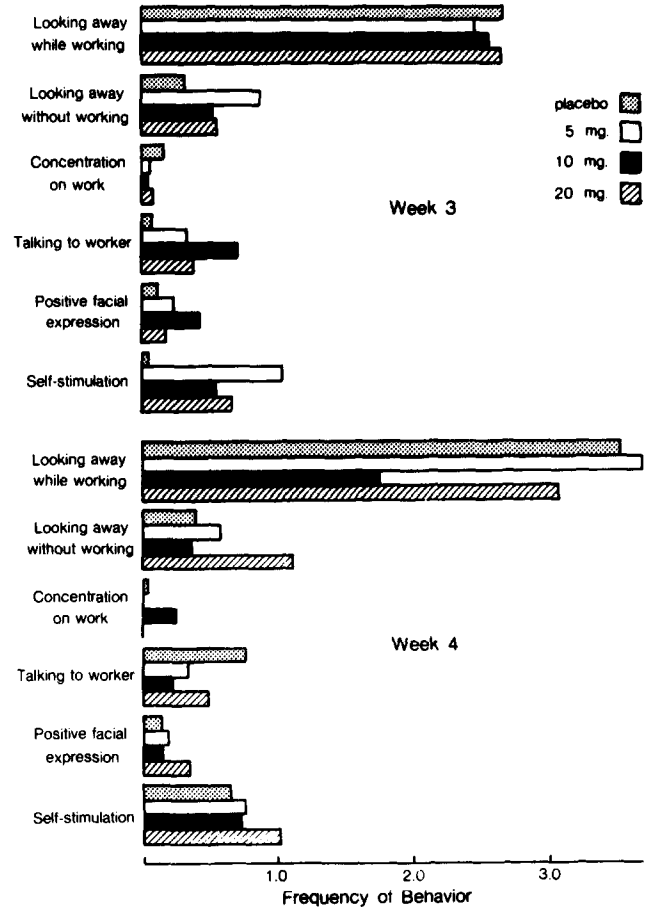


FIG. 4. Profile of behavioral frequency during weeks 3 and 4 as a function of dose.

2a, indicate that different patterns of behavior predicted productivity at each dosage. Several of the findings are striking. First at the higher doses (10 and 20 mg) there is a greater relationship between behavior and performance. Second, the relationship between "looking away without work" and productivity, which accounted for most of the variance, carried opposite signs for the low (0, 5) and high (10, 20) doses. Third, although many behaviors were held in common there were distinctive differences among the doses (Table 2a). For instance, treatment with the peptide resulted in a greater relationship between touching and work than placebo. Conversely walking away from work was more predictive of performance when clients received placebo than when they received any dose of the peptide. Further there were several behaviors which were particular for a certain dose. Gesturing characterized 10 mg, supervisor contact was related to 5 mg and doing nothing was related to placebo and 20 mg. Indeed, consistent with previous analysis, marked similarities existed between 0 and 20 mg with only touching behavior identifying 20 mg with the other doses of the peptide.

Since either "looking away without working" or "concentration on work" accounted for the majority of variance at each dosage a second analysis was conducted excluding these variables to elucidate further differences between behavior and productivity as a function of dose of the MSH/ACTH 4-9 analog. The results are presented in Table

TABLE 2

Dosage	Behavior	R	$\beta$	p
2a				
Multiple Stepwise Regression of the Relationship Between Behavior and Resistor Produced for Each Dosage				
Placebo	2. Looking away w/out working	.26	-.17	.001
	4. Concentration on work	.33	-.24	.001
	12. Walking away from work area	.35	-.12	.001
	1. Looking away while working	.38	.13	.001
	3. Doing nothing	.40	-.15	.001
5 mg	2. Looking away w/out working	.28	-.24	.001
	19. Self-stimulation	.34	.17	.001
	17. Being touched by others	.38	.18	.01
	9. Supervisor talks to client	.42	-.17	.01
10 mg	4. Concentration on work	.32	-.14	.001
	14. Gestures (hand, body, head)	.35	.31	.01
	17. Being touched by others	.38	.15	.01
	2. Looking away w/out working	.41	.16	.01
20 mg	2. Looking away w/out working	.45	.20	.001
	4. Concentration on work	.52	-.32	.001
	1. Looking away while working	.57	-.14	.001
	18. Touching others	.59	.32	.01
	3. Doing nothing	.60	-.13	.01
11. Restless movement	.61	-.14	.01	
2b				
Multiple Stepwise Regression of the Relationship Between Behavior and Resistor produced for Each Dosage Excluding Behaviors 2 and 4				
Placebo	3. Doing nothing	.17	-.17	.01
	12. Walking away from work area	.22	-.16	.01
	1. Looking away while working	.27	-.17	.01
	19. Self-stimulation	.30	-.14	.01
5 mg	19. Self-stimulation	.23	-.16	.01
	9. Supervisor talks to client	.29	.21	.01
	17. Being touched by others	.35	.19	.01
	1. Looking away while working	.38	.10	.01
10 mg	19. Self-stimulation	.17	-.18	.01
	1. Looking away while working	.23	-.18	.01
	5. Unccordination	.27	-.15	.01
	14. Gestures (hand, body, head)	.30	.14	.01
20 mg	19. Self-stimulation	.31	-.26	.001
	3. Doing nothing	.36	-.20	.01
	18. Touching others	.40	-.17	.01
	11. Restless movement	.43	-.15	.01

2b. The most dramatic finding is that self stimulation is the best predictor of productivity for each of the three doses of the peptide. Touching behavior distinguishes the 5 and 20 mg dose from the placebo and gesturing is characteristic only of the 10 mg dose.

#### Group Classification

A stepwise discriminant function analysis [5] was employed to discriminate the effects of the 4 doses of the peptide analog. In this analysis the dependent variables (resistor production and the 19 behaviors) are considered, one at a time, to determine which variables yield the best discrimination among the 4 doses. Consistent with the other analyses the 4 doses of the peptide analog could be significantly discriminated from each other. Although many of the variables entered the discriminant function, the 3 variables which contributed most to the discrimination were resistor productivity, looking away while working and self stimulation. Although these variables were statistically significant when entered into the discriminant function, the percentage of cases classified correctly with jackknifing procedures was less impressive. Prediction of group membership for placebo and 5 mg was not better than chance. However, for the higher doses, 10 and 20 mg, the accuracy of group classification was about twice as good as chance. Thus the statistical effects may be attributed to the unique patterns of behavior generated by 10 and 20 mg of the ACTH 4-9 analog.

#### DISCUSSION

The results of this study add a new dimension to the catalogue of effects of MSH/ACTH fragments in human behavior. While augmented environmental attention has been reported previously [8,9] the increase in interpersonal awareness and communication following treatment with MSH/ACTH fragments has not been observed. During the first week of treatment with the peptide clients became more gregarious and sociable. Although these behaviors have not been observed previously in human subjects, rats treated with MSH are more gregarious, as measured by body contact, than their placebo-treated siblings [1]. Further, laboratory studies of human subjects have reported reliable decreases in anxiety following treatment with MSH/ACTH fragments [6, 8, 9]. It is consistent that decreases in anxiety would be associated with improved interpersonal relations, however, little attention has been focused on this aspect of the influence of the peptide. Since there is rarely an opportunity to observe complex social behavior in the laboratory, this is the first report of MSH/ACTH affecting interpersonal behavior.

The pattern of results changed during the second week of treatment with the peptide. The differences in social behavior among the groups stabilized while productivity increased for clients receiving the peptide. After taking the peptide, clients were more distracted by the extraneous activities of the workshop than when given the placebo. Ironically, however, productivity increased apparently due to the fact that when they worked the clients worked with greater conscientiousness and intensity. These data can be reconciled with laboratory findings that normal and retarded subjects evidence enhanced orienting responses to novel stimuli and also retain the ability to discriminate relevant from irrelevant information after treatment with MSH/ACTH 4-10 [8, 9, 10].

The illusive dose relationship between peptides and behavior was vividly illustrated in this study (see Fig. 2). Spe-

cific behaviors appeared to be discretely tied to certain doses of the peptide. Although 10 mg of the MSH/ACTH 4-9 analog was the optimal dose for productivity, as the work required greater precision both 5 and 10 mg became increasingly effective. Conversely, 20 mg interfered with performance of all steps of the task. Patterns of behavior also reflected dosage relationships. Concentration on work typified clients receiving 10 mg during week 4 whereas distraction was more common among clients receiving 20 mg. Since few reports of dose relationships for MSH/ACTH fragments exist [2], these findings constitute important psychopharmacological evidence for the eventual application of these

compounds for behavioral problems.

The findings of this study indicate that an analog of endogenous peptides can facilitate interpersonal and environmental awareness. The converging array of results suggest that the peptide fragments related to ACTH and MSH have a beneficial influence on behavior without any known side effects. For instance these compounds do not stimulate the release of corticosterone (which is stimulated by ACTH 1-24), or of other steroids and hormones [8, 9, 13]. The use of these peptides with patient groups to facilitate interpersonal and environmental awareness is encouraged by our findings.

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