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Neuropeptide MSH/ACTH 4-10 Enhances Attention in the Mentally Retarded

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SANDMAN, C. A., J. GEORGE, B. B. WALKER, J. D. NOLAN AND A. J. KASTIN. *Neuropeptide MSH/ACTH 4-10 enhances attention in the mentally retarded.* PHARMAC. BIOCHEM. BEHAV. 5: SUPPL. 1, 23–28, 1976. - Twenty adult mentally retarded men were randomly assigned to receive MSH/ACTH 4-10 or a vehicle control solution in a double blind procedure. After an intravenous injection the subjects were presented with an orienting sequence and a series of behavioral tests. Treatment with the peptide resulted in a significant decelerative heart rate response during the test stimulus of the orienting sequence. Improved performance of the intradimensional and extradimensional shift of a visual discrimination procedure was significant for subjects receiving MSH/ACTH 4-10. The pattern of response on the subproblem analysis of the extradimensional shift reflected greater dimensional attention in the subjects treated with the peptide. Attentive subjects given MSH/ACTH 4-10 evidenced significant improvement on a rhythm matching test, a test of spatial localization and a visual retention test. The data were interpreted as indicating that the peptide resulted in improved attention of stimulus processing. It was speculated that MSH/ACTH 4-10 may be uniquely coded for perceptual/attentional functioning and may be useful as a treatment for disorders of attention.

Behavioral effects of peptides Attention Mentally retarded Orienting response Disorders of attention Concept learning

RECENT evidence in rats [5,8] and in human subjects [2, 6, 7] has suggested that the fraction of MSH and ACTH which share the heptapeptide, Met-Glu-His-Phe-Arg-Trp-Gly (MSH/ACTH 4-10), enhance selective attention and perceptual processing. For instance, rats administered MSH or its analogues perform significantly better on the reversal shift of a visual discrimination problem [5,8]. Analogous research with healthy human subjects had indicated that treatment with MSH/ACTH 4-10 improves performance of the intradimensional shift [6] and selectively facilitates learning of the changed dimension of the extradimensional shift in a visual discrimination procedure [7]. Further, augmented oriented responses, improvement of visual memory in tasks with attentional demands and increased capacity to discriminate tachistoscopically presented stimuli have been related to administration of MSH/ACTH 4-10 in normal human subjects [7].

Mentally retarded patients often perform poorly on tasks involving discrimination shifts and their poor performance on such tasks has been attributed, at least in part, to "attentional" factors [4,10]. Earlier studies with rats [5,8] indicated that visually or attentionally deficient animals evidenced a relatively larger improvement in attention than non-deficient animals after treatment with MSH. Thus it was of interest in the present study to determine the impact of MSH/ACTH 4-10 on attentional processes in a population of human subjects who are greatly compromised in attentional ability.

METHOD

Subjects

Mentally retarded adult men, ages 20–42, were recruited from workshops for the trainable retarded. The prospective subjects were given a complete demonstration of the procedure and then interviewed for comprehension of the experiment and interest in participation. Those who understood (as assessed by several content related questions) and expressed an interest in participating, signed a consent sheet. Informed consent was also obtained from their legal guardians. The subjects received payment which was equivalent to the wage they would have earned if they remained at the workshop and earned an average wage. All of the subjects were further screened for general good medical health, lack of drug maintenance, and absence of grand mal seizure activity. Of the fifty-five subjects screened, twenty were selected to participate in the study.

Procedure

The subjects were transported to the laboratory and tested in a sound attenuated chamber between 9–11 a.m.

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All of the equipment was housed in an adjacent control chamber. During the initial phase of the experiment they reclined in a comfortable chair, and they were allowed to accommodate to the laboratory while electrodes for measuring heart rate were attached. After the period of accommodation half of the subjects were randomly assigned to receive a 15 mg, IV injection of MSH/ACTH 4-10 (OI63, Organon, OSS, the Netherlands) and half were assigned to receive a vehicle control solution (10 ml in 0.9% NaCl) in a double blind procedure. Fifteen minutes following the injection a standard orienting sequence was presented. Twelve green slides were projected into the chamber for 2 sec each with an intertrial interval of 30 sec. On the thirteenth presentation a red slide appeared (test stimulus) and it was repeated for a total of twelve presentations.

The visual discrimination procedure was presented by means of the Wisconsin General Test Apparatus 30 min after the injection. Each subject was trained on a two-choice problem with one relevant dimension (e.g., color) and one irrelevant dimension (e.g., shape). After acquiring the original discrimination (10 consecutive correct), the subject learned, in succession, reversal, intradimensional and extradimensional shifts. For example, if color (e.g., red) was reinforced for the original problem, during the reversal procedure color remained the relevant dimension but the opposite value (e.g., green) was reinforced. On the intradimensional shift, a new set of stimuli differing in both shape and color was introduced, but color remained the relevant dimension (e.g., blue was reinforced). For the extradimensional shift, a value of the formerly irrelevant dimension of shape (e.g., square) was reinforced.

The Benton Visual Retention Test was administered in its standard form. Ten increasingly complex geometric figures were presented to the subject for five seconds and then removed from view. Fifteen seconds later the subjects were instructed to reproduce the figure from memory on a plain sheet of paper. The performance of the mentally retarded subject was very poor and not scorable with traditional procedures. The forms were divided into simple and complex figures and points were awarded for the number of details accurately reproduced.

Several tests from the Halstead-Reitan neuropsychological battery were administered including: Trails, Finger Tapping, Tactile Recognition, Rhythms and Astereognosis. The Trail B test requires that the subject connect a series of points in order by alternating between numbers and letters. For instance, the subject should connect 1 with A and A with 2 and 2 with B, etc. The test requires that the subject work with two sets of information simultaneously and continue to alternate between them. For the finger tapping test the subject is instructed to depress a lever, which is attached to a mechanical counter, as fast as possible. Five trials each are administered for the dominant and nondominant hand. The tactile recognition test involves the subject's ability to determine, without benefit of visual cues, which of his fingers the experimenter touches and he must also recognize numbers written on this hand. The rhythm test requires that the subject listen to, and compare two rhythms. In the test of astereognosis the subject is given a geometric shape to hold in one hand while his vision is obscured and point with his other hand to a match from a set of four visually presented geometric forms.

RESULTS

Basal heart rate declined significantly, $F(2,26) = 5.12$, $p<0.01$, throughout the course of the experiment probably reflecting habituation to the experimental situation. The changes in basal heart rate were not specific for either subjects treated with MSH/ACTH 4-10 or the control solution. However subjects treated with MSH/ACTH 4-10 evidenced a significant, $F(4,48) = 2.71$, $p<0.05$, decelerative heart-rate response to the test stimulus during the orienting sequence (Fig. 1). Subjects treated with the control solution had an initial heart-rate increase followed by a biphasic response pattern.

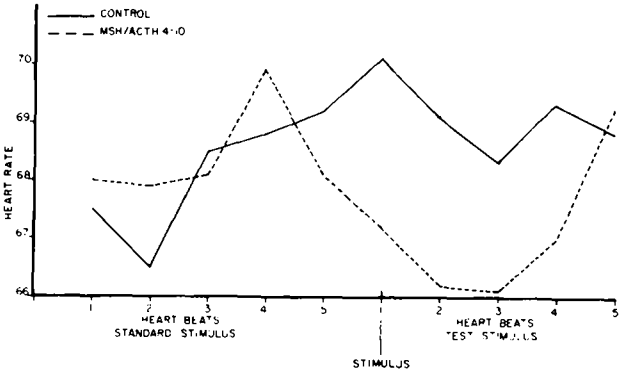

FIG. 1. Heart rate for each of 5 beats during the last stimulus of a standard sequence (habituated response) and the first stimulus of a test sequence (orienting response).

As illustrated by Fig. 2 treatment with MSH/ACTH 4-10 improved the subjects performance on all but the original problem of a visual discrimination sequence. Performance of the intradimensional and extradimensional shift were significantly improved after treatment with the peptide fragment. As illustrated in Fig. 3, treatment of subjects with MSH/ACTH 4-10 significantly, $F(1,11) = 6.20$, $p<0.03$, improved their performance of the intradimensional shift. The performance of subjects treated with the control solution was opposite to that of subjects receiving MSH/ACTH 4-10.

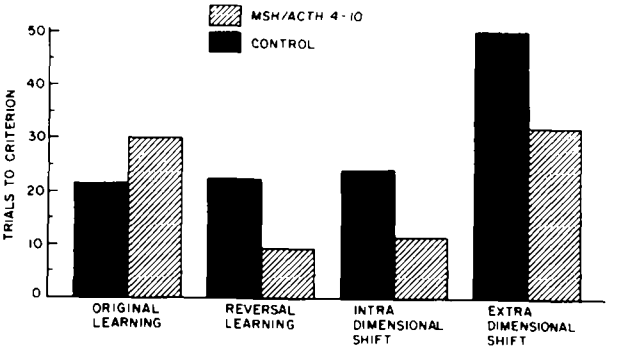

FIG. 2. Trials to criterion during original learning and the reversal, intradimensional and extradimensional shift in mentally retarded subjects receiving MSH/ACTH 4-10 on the vehicle control solution.

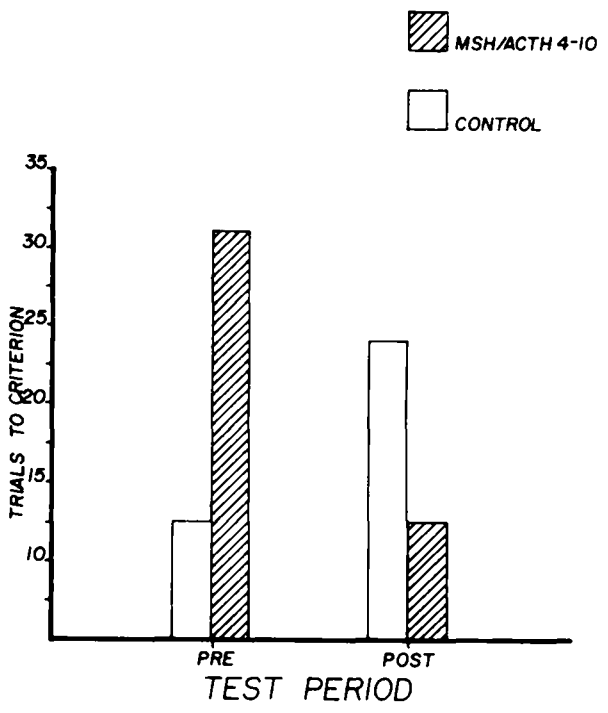

FIG. 3. Trials to criterion on the intradimensional shift before and after treatment with MSH/ACTH 4-10 or the vehicle control solution.

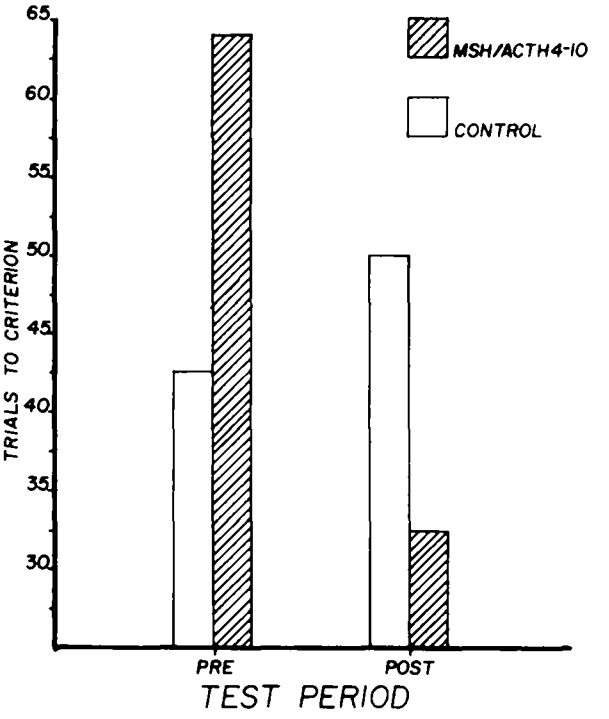

FIG. 4. Trials to criterion on the extradimensional shift before and after treatment with MSH/ACTH 4-10 or the vehicle control solution.

It is apparent from Fig. 4 that the subjects treated with MSH/ACTH 4-10 improved dramatically on the extradimensional shift, $F(1,11) = 5.02$, $p < 0.05$. Performance of the shift after treatment with the peptide was completed in half as many trials as before treatment. The performance of subjects given the control solution was opposite to that of the subjects treated with the peptide. Even though the subjects were randomly assigned to groups there were initial differences between the groups. However, the pre-to-post differences for the control groups were not statistically reliable for either the intradimensional or the extradimensional shift.

As described by Tighe, Glick and Cole [9] the extradimensional shift can be divided into two subproblems. In one, the unchanged problem, the positively reinforced stimulus during the extradimensional shift corresponds to the stimulus previously reinforced during the intradimensional shift. For instance, if yellow stimuli were reinforced during the intradimensional shift and if triangular shapes were reinforced during the extradimensional shift, then yellow triangles could be responded to because of color, shape or as specific stimuli not necessarily representative of a dimension. During the changed subproblem the positive stimulus of the extradimensional shift does not correspond to the stimulus reinforced during the intradimensional shift. The subject must learn that blue triangles are also representative of the new correct concept, triangularity, and that the dimension of shape and not color is correct. If a subject responds to a stimulus as representative of a dimension (i.e., shape) and not as separate stimuli (i.e., yellow triangles) then no differences between the initial responses to the changed and unchanged stimulus pairs would be expected.

From Fig. 5 it can be seen that groups treated with

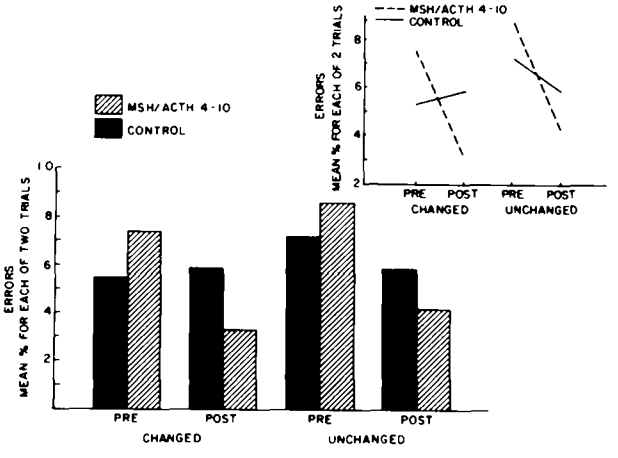

FIG. 5. Percentage of correct responses for blocks of two trials on the changed and unchanged subproblem analysis of the extradimensional shift. The smaller graph illustrates the significant interaction.

MSH/ACTH 4-10 respond differently during the changed and unchanged subproblems than subjects receiving the control solution. The differences for the changed dimension were statistically significant ($\chi^2 = 7.76$, $df = 1$, $p < 0.01$) since performance was best after treatment with the peptide. Sign tests conducted for each group revealed that the improvement in performance was significant only for the subjects treated with the peptide (changed problem, $p < 0.01$; unchanged problem, $p < 0.03$).

Figures 6 and 7 clearly indicate that the differences between the groups on the extradimensional shift after

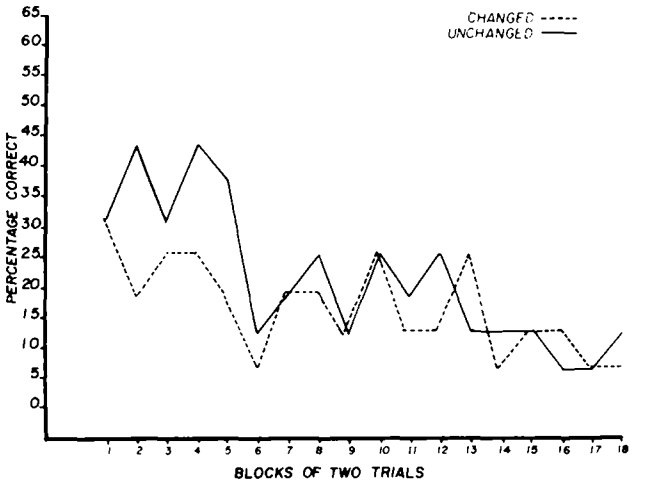

FIG. 6. Percentage of correct responses for the changed and unchanged subproblems of the extradimensional shift for subjects treated with MSH/ACTH 4-10. (The apparent decline in the performance curves is due to the fact that only the slowest subjects remained after trial block 6).

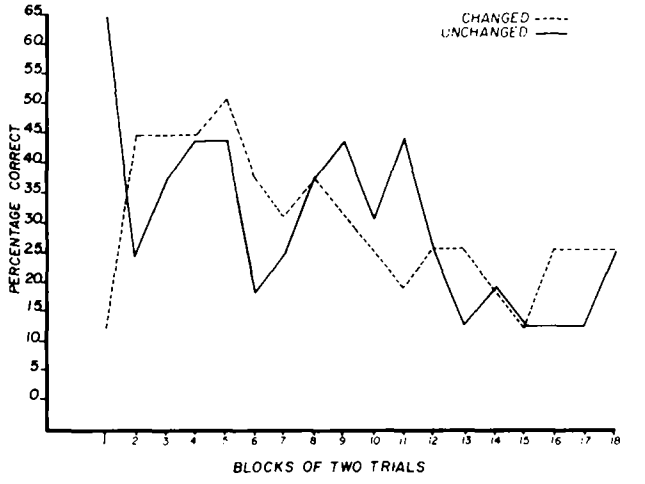

FIG. 7. Percentage of correct responses for the changed and unchanged subproblems of the extradimensional shift for subjects given the vehicle control solution.

treatment with either the peptide or the vehicle solution is due to the initial response to the subproblems. The subjects treated with MSH/ACTH 4-10 (Fig. 6) evidence virtually no differences in responding to the changed and unchanged problems. According to the logic developed by Tighe *et al.* [9] the data for subjects given the MSH/ACTH 4-10 peptide indicate that they are responding attentionally. The mentally retarded subjects given the control solution (Fig. 7) apparently respond to the stimulus pairs as separate stimuli (yellow triangles – blue triangles) and not dimensionally.

The differences, $F(1,11) = 6.08$, $p<0.05$, in the test of astereognosis (Fig. 8) is due to the improvement in performance of the control subjects. The subjects given the peptide showed no change in performance. Since the subjects given MSH/ACTH 4-10 performed very well in the

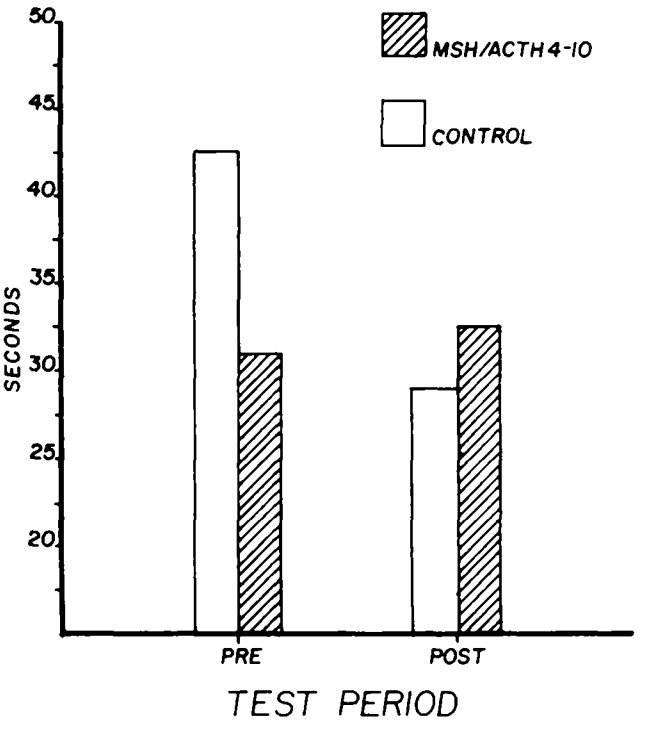

FIG. 8. The time required to match tactile stimuli with a visually displayed set of stimuli.

pretest condition, improvement may have been limited by a ceiling effect.

Based upon the pretesting data for the intradimensional shift, the subjects were placed in either attentionally deficient or nondeficient groups. Consistent with the reasoning of Nolan [3], solution of the intradimensional shift in two or less trials is related to attentionally efficient responding. Subjects requiring more than two trials to solve the intradimensional problem were placed in the attentionally deficient group. Four groups of 5 subjects each were generated. The remaining analyses were performed with attention as a factor.

Several interactions between treatment with peptide and attentional responding were detected. It is apparent from Fig. 9 that attentive subjects treated with MSH/ACTH 4-10 made fewer errors, $F(1,12) = 5.29$, $p<0.05$, on the rhythms test than subjects given the control solution. Additionally attentive subjects given MSH/ACTH 4-10 made significantly fewer errors on the Trials B test, $F(1,12) = 8.85$, $p<0.01$, (Fig. 10) and performed significantly better on the complex figures of the Benton Visual Retention Test, $F(1,12) = 4.55$, $p<0.05$, (Fig. 11) than subjects given the vehicle solution.

DISCUSSION

In this first controlled study of a patient population it was clearly demonstrated that MSH/ACTH 4-10 has a significant influence on behavior. Consistent with findings in healthy, human volunteer subjects [6,7], the mentally retarded subjects receiving MSH/ACTH 4-10 significantly improved on the intradimensional shift and responded in a dimensionally attentive manner according to the subproblem analysis of the extradimensional shift. The peptide also resulted in a significant heart deceleration to the test

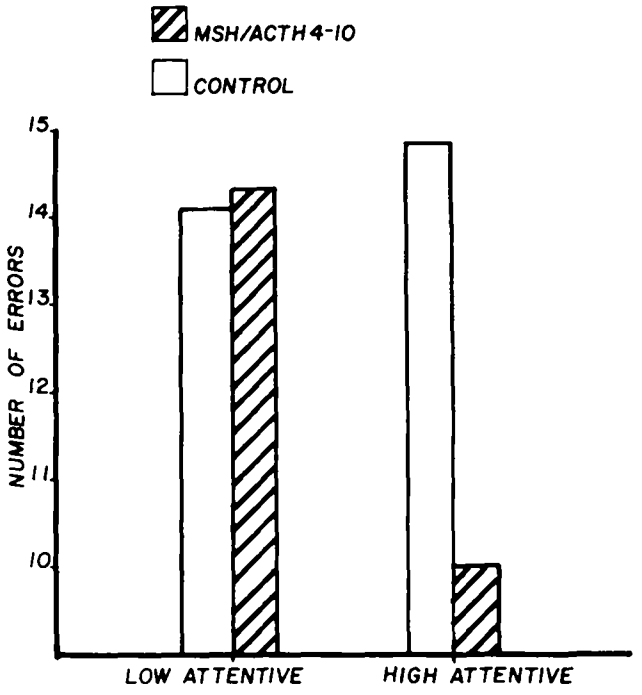

FIG. 9. The number of errors made in comparing aurally presented rhythms in low and high attentive subjects given either MSH/ACTH 4-10 or the control solution.

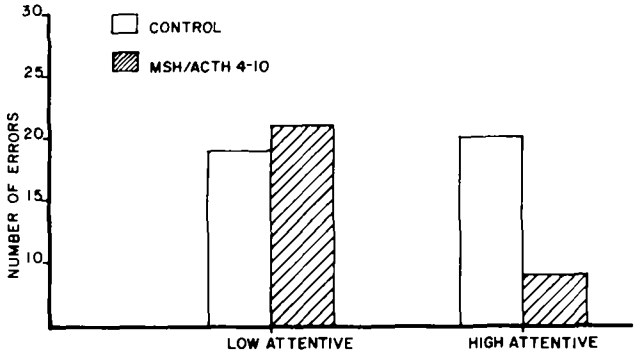

FIG. 10. Performance of attentive and unattentive mentally retarded subjects on the Trails B tests after treatment with MSH/ACTH 4-10 or the vehicle control solutions.

stimulus of an orienting sequence. It has been suggested that heart-rate deceleration is a sensitive measure of orienting tendencies and that the response may serve to lower threshold for environmental stimulation [1]. Administration of the peptide did not result in a decrement of performance on any of the tests administered and appeared to improve performance primarily on tests with attentional demands.

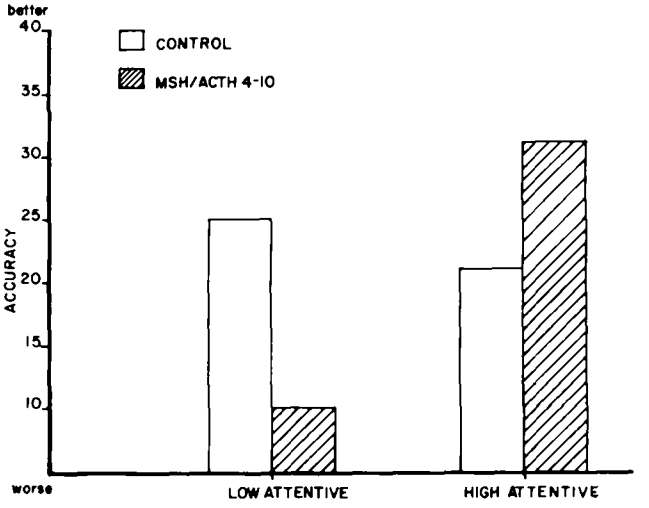

FIG. 11. Accuracy of performance of mentally retarded subjects on the complex figures of the Benton Visual Retention Test after treatment with MSH/ACTH 4-10 or the vehicle control solution.

The finding that MSH/ACTH 4-10 dramatically improved the performance of attentional subjects support the explanation that the peptide may influence attention. On three tests, not directly related to attention, attentive subjects given the peptide, evidenced significant improvement. While these data suggest that certain subgroups of the mentally retarded population may improve their performance on a variety of tasks after treatment with MSH/ACTH 4-10, interpretation of these data must be tempered by the relatively small number of subjects in each group with this analysis and the possible confounding of pretest and posttest scores.

The pattern of results obtained in this study strongly indicate that one injection of the heptapeptide, MSH/ACTH 4-10, improves attention or stimulus processing in a group of subjects severely deficient in this ability. These data together with those collected in rats [5,8] and healthy human subjects, [2, 6, 7] suggest that the predominant neuropeptide effect of MSH, ACTH and their analogues may be to improve selective attention. It is conceivable that the behaviorally active chain of the MSH and ACTH molecules are uniquely coded for attentional-perceptual functioning. If this is true then disorders of attention, evident in some forms of schizophrenia, psychopathy and mental retardation, may be ameliorated by administration of MSH/ACTH fragments.

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