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Neuroheptapeptide Influence on Attention and Memory in Man

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MILLER, L. H., L. C. HARRIS, H. VAN RIEZEN AND A. J. KASTIN. *Neuroheptapeptide influence on attention and memory in man.* PHARMAC. BIOCHEM. BEHAV. 5: SUPPL. 1, 17–21, 1976. – Twenty normal, male volunteers were administered a subcutaneous injection of either ACTH/MSH 4–10 or diluent and two weeks later received the alternate injection in a complete crossover, double-blind design with order balanced. Subjects were given a battery of psychological tests, including a continuous performance task (CPT), following each injection. Visual evoked responses were recorded during the CPT. Resting, eyes-closed EEGs were also obtained. ACTH/MSH 4–10 improved attention and in so doing improved visual-motor learning and visual, but not verbal, memory. EEG data were consistent with activation of the diffuse thalamic projection system.

ACTH/MSH 4–10 Attention Vigilance Memory Learning Heart rate GSP EEG Evoked potentials

SHORT-CHAIN polypeptides such as adrenocorticotropic hormone (ACTH) and melanocyte stimulating hormone (MSH) and their fractions have been consistently shown to have striking effects on both behavior and electrophysiological activity in man and lower animals. The heptapeptide comprising ACTH/MSH 4–10, for instance, has been demonstrated to enhance visual memory [9,12] facilitate intradimensional shifts in concept formation [15] and reduce anxiety [12] in man. In the rat, this heptapeptide renders active and passive conditioned avoidance [3, 4, 17] and appetitive [16] behaviors highly resistant to extinction. It also facilitates reversal learning [14] but interferes with conditional learning [21] in the rat.

In a mixed group of human subjects with hypopituitarism of varying etiology, synthetic αMSH has been shown to interact with the attentional demands of a simple reaction time procedure to dramatically increase the magnitude of the somatic evoked potential [9] and to enhance visual, but not verbal, memory. Endroczi [5] has shown that ACTH 1–24 and ACTH 1–10 facilitate the recovery of a stimulus specific EEG arousal pattern in man. ACTH 4–10 has been shown by Miller *et al.* [12] to effectively reinstitute a previously habituated αblocking response during the interstimulus interval of a fixed foreperiod disjunctive reaction time task and to produce a generally more activated EEG also in human subjects.

A number of psychological and metaphysiological constructs have been forwarded as unifying explanations of the behavioral and electrophysiological effects of MSH/ACTH 4–10. Emotionality [21], memory [3,4], and attention [12,18] have all been explored, at one time or another, but, at the moment, influences on attention appear to be the most parsimonious explanation of the behaviors that have been observed. To date, however, no one has examined the effects of this neuroheptapeptide on an explicitly attentional task in such a way as to systematically relate such behavior to the electrophysiological activity of the sensory system involved. The study reported here was designed primarily as a test of an attentional explanation of the ACTH/MSH 4–10 effects on brain function and behavior in man.

METHOD

Twenty, healthy, young, paid, male volunteers were recruited from the student population at Temple University School of Medicine. All subjects were screened by physical and psychiatric examination and were given Witkin's rod and frame test [26] and Spielberger's State-Trait Anxiety Inventory [20]. Only low anxious, field-independent subjects were included in the study [1]. Subjects were randomly assigned to either ACTH 4–10–Saline or Saline–ACTH 4–10 sequences in a complete crossover, double-blind design with order balanced.

Procedure

Subjects arrived at the laboratory at 7:45 a.m. and were taken to an electrically shielded, sound-attenuated room where they were seated in a comfortable reclining chair. Grass silver cup electrodes were attached with Grass electrode cream at O_1 and O_2 (International 10–20 System) referenced to ipsilateral mastoid. Electrodes for Galvanic Skin Potential (GSP) and heartrate were also applied at this time.

Subjects were given instructions to look at an oscilloscope screen upon which letters would appear and to press

a key whenever the letter *X* appeared. The letters were generated by a PDP-12 computer in such a way that the more accurate the performance, the shorter the interval between letters and the shorter their duration. There were four levels of difficulty in this modification of Rosvold and Mirsky's [13] continuous performance task (CPT). Level 4, the most difficult level, had an interstimulus interval (ISI) of 800 msec and a stimulus duration (SD) of 100 msec.

Following a 15 min warmup session on a CPT with a ratio of 1 relevant stimulus (*X*) in two, Ss received a subcutaneous injection of either 30 mg ACTH 4–10 or saline and rested quietly for 20 min. Subjects were then readministered the 1:2 CPT plus 1:5, 1:9, and 1:13 CPTs with 2 min rest periods interspersed between. At the conclusion of the postinjection CPT runs, Subjects were administered: (1) Benton Visual Retention Test [2]; (2) Wechsler Memory Scale [24]; (3) Digit Symbol Substitution [25]; (4) State-trait Anxiety Inventory [20]; (5) Subjective State Questionnaire; and, (6) Rod and Frame [26].

After an interval of two weeks, subjects returned to the laboratory, received the alternate of their first injection, and were administered alternate forms of the various tests within a format identical to that of the first session.

CPT scores were calculated as % times at level 4 (most difficult level). All other tests were scored in the manner prescribed for each test.

Averaged evoked potentials were obtained from right and left occipital areas for the relevant and nonrelevant stimuli under both ACTH 4-10 and saline conditions. Galvanic skin potential and heartrate were recorded continuously. Eyes closed, resting EEGs were obtained for off-line power spectral analysis during inter-CPT rest periods.

RESULTS

The CPT data presented in Table 1 indicate that ACTH/MSH 4–10 only improved objective attentional behavior to a significant degree ($p<0.05$) at the time of the first shift in the ratio of relevant stimuli to non-relevant stimuli. It is apparent that a ceiling effect was in operation as the subjects performed very well even on the control saline runs. Only at the time of the greatest attentional demand (i.e., subjects had to attend while developing new expectancies) was the excellent performance on control runs significantly exceeded by performance on the ACTH/MSH 4–10 runs.

The pattern of CPT errors as shown in Table 2 demonstrated that the improvement in performance on the 1/5 CPT shown during the ACTH/MSH 4–10 runs was not merely a function of an increased response rate such as one might expect with an amphetamine-like substance. Whilst errors of omission were significantly reduced ($p<0.05$) during ACTH/MSH 4–10 runs, errors of commission were also fewer, but not significantly so. This would suggest that ACTH/MSH 4-10 has a highly selective effect on attentional mechanisms rather than a generalized activating effect.

Visual evoked potential data (Fig. 1) further support the suggestion that ACTH/MSH 4–10 influences the attentional mechanisms associated with performance on the CPT. ACTH/MSH 4–10 served to significantly ($p<0.05$) increase the latency and decrease the magnitude of the negative component occurring at around 200 msec. In addition, visual evoked potentials from the ACTH/MSH 4–10 runs contained an additional negative element

TABLE 1

AVERAGE PERCENTAGE OF TIME SPENT AT THE MOST DIFFICULT LEVEL OF THE CPT DURING THE VARIOUS RATIOS OF RESPONSE/NONRESPONSE CONTINGENCIES. ONLY THE 1/5 SECTION POST INJECTION SHOWED A SIGNIFICANT PEPTIDE IMPROVEMENT OVER SALINE RUNS.

CPT

% Time Level 4

	ACTH$_{4-10}$		Saline		tdiff
	$\bar{X}$	S.E $\bar{X}$.	$\bar{X}$	S.E.$\bar{X}$.	df=19
Pre					
1/2	92.79	1.31	91.32	1.95	1.01
Post					
1/2	93.75	1.13	92.11	1.78	1.25
1/5	94.35	59	91.10	1.81	2.03*
1/9	90.47	1.76	88.85	2.93	1.14
1/13	93.00	.67	92.58	.58	.52

* p .05

TABLE 2

THE PATTERN OF ERRORS INDICATES THE IMPROVED PERFORMANCE ON THE 1/5 CPT DURING ACTH 4–10 RUNS WAS DUE TO DECREASES IN BOTH THE NUMBER OF ERRORS OF OMISSION AND COMMISSION.

Errors of Omission

	ACTH$_{4-10}$		Saline		tdiff
	$\bar{X}$	S.E.$\bar{X}$.	$\bar{X}$	S.E.$\bar{X}$.	df=19
Pre					
1/2	5.47	1.68	9.84	3.31	−1.75
Post					
1/2	3.85	1.61	6.58	2.76	− .98
1/5	1.10	.31	3.20	1.31	−1.81*
1/9	1.21	.45	1.90	1.24	− .71
1/13	.68	.33	.58	.18	.28

CPT

Errors of Commission

Pre					
1/2	5.58	1.12	4.32	.76	1.03
Post					
1/2	4.80	1.25	5.11	.87	− .20
1/5	.95	.29	1.35	.33	−1.14
1/9	1.16	.62	.95	.34	.24
1/13	.26	.17	.53	.19	−1.05

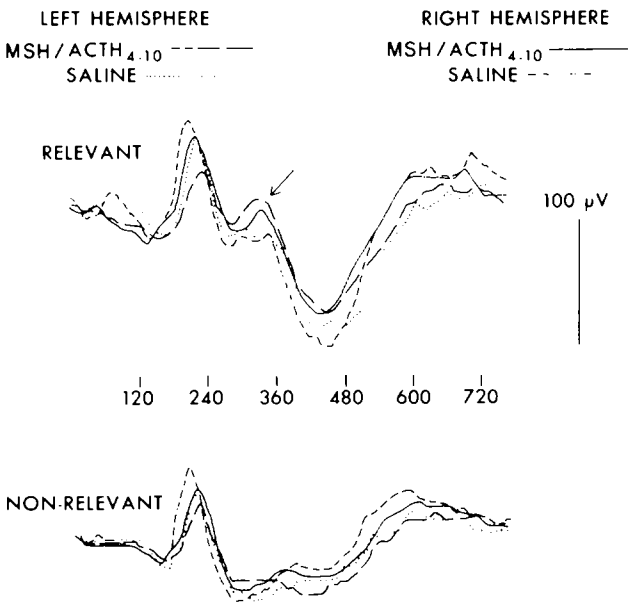

FIG. 1. Averaged evoked visual responses of left and right hemispheres (O_1 and O_2 referenced to ipsilateral mastoid) to relevant and non-relevant stimuli of 1/5 CPT for MSH/ACTH4-10 and saline control runs.

(arrow) at around 350 msecs that was not present during the control runs. As it occurred in 17 of the 20 subjects during ACTH/MSH 4--10 runs and in none of the control (saline) runs, the presence of this additional negative component cannot be attributed to an artifact of averaging [3].

Visual and power spectral analysis of eyes-closed, resting EEGs taken during the inter-CPT rest periods indicated a tendency toward lower amplitude and faster frequency alpha activity under the influence of ACTH/MSH 4-10. Slower frequencies also tended to drop out during experimental, but not control, runs.

Post-CPT psychological test data (Table 3) indicate that ACTH/MSH 4–10 influences a host of behaviors associated with a variety of psychological constructs. The memory quotient (MQ) from the Wechsler Memory Scale was significantly ($p<0.05$) higher for the ACTH/MSH 4-10 runs. Another finding related to memory was made on the Benton Visual Retention Test where the number of correct reproductions was significantly ($p<0.05$) higher [2] on the ACTH/MSH 4 10 runs. Improved ($p<0.05$) performance on the Digit Symbol Substitution Test would, on the other hand suggest a peptide influence on visual-motor learning.

A breakdown of the Wechsler Memory Scale into its components reveals a highly selective effect of this neuroheptapeptide on the mnemonic process. Visual memory (visual reproductions) was improved significantly ($p<0.05$) by the peptide as was memory for digits (digits total).

TABLE 3

PSYCHOLOGICAL TEST DATA INDICATE A SIGNIFICANT PEPTIDE INFLUENCES ON A HOST OF PSYCHOLOGICAL CONSTRUCTS.

PSYCHOLOGICAL DATA N=20					
	$ACTH_{4-10}$		Saline		tdiff
Variable	$\bar{X}$	S.E.$\bar{X}$.	$\bar{X}$	S.E.$\bar{X}$.	df=19
Wechsler Memory	61.10	1.26	58.45	1.48	1.74*
Mental Control	8.65	.18	8.45	.33	.57
Memory Passages	11.53	.52	11.58	.67	−.74
Digits Total	13.35	.39	12.75	.36	1.79*
Visual Reproductions	10.10	.48	9.00	.57	1.74*
Paired Associates	17.48	.59	16.68	.61	1.30
Digit Symbol	75.23	2.04	72.55	1.76	2.01*
Benton (Correct)	7.65	.27	6.90	.38	2.03*
Benton (Errors)	3.00	.48	4.50	.67	−2.57**
Rod and Frame	1.86	.19	1.84	.20	.23
Trait Anxiety	33.05	1.38	33.00	1.29	
State Anxiety	36.55	2.22	32.95	1.24	1.69

** $p<.01$
* $p<.05$

Associative verbal learning (paired associates) did appear to be influenced in a favorable direction but not to significant degree.

Field dependency scores (rod and frame) were not influenced by the peptide. State anxiety scores were elevated to a nonsignificant degree, but remained well within the low-anxious range.

DISCUSSION

While portions of the behavioral data would be consistent with a peptide influence on memory, the weight of the evidence favors an influence on attentional processes. The memorial data could be explained on the basis of an attentional hypothesis in that it was those elements of the Wechsler Memory Scale which required immediate, focussed attention and were not subject to subvocal rehearsal that were improved by the peptide.

The finding of improved visual, but not verbal, memory following ACTH/MSH 4–10 administration has previously been reported by our group [9] and appears to be a general effect across a variety of subjects. To impute this effect to a selective influence on specific aspects of the mnemonic process would require the postulation of function-structure relationships for which there would be little support in the literature.

The visual evoked response data are quite consonant with the existing literature on peptide influences on electrocortical activity and further support the attentional hypothesis. Urban *et al.* [22] have shown ACTH/MSH 4–10 to elicit hippocampal theta activity in the boxer dog and Adey [1] and Van Leeuwen *et al.* [23] have demonstrated that hippocampal theta activity accompanies vigilance behaviors in a variety of species. Further evidence in the inferential chain deals with the reciprocal relationship between hippocampal theta and late components of the visual evoked response [6, 7, 8, 11, 19]. That is, the greater the theta, the smaller the late components. While hippocampal recordings were not obtained in this study, the visual evoked response data are consistent with the postulated peptide influence on neural substrates of attentional processes which would include the hippocampus.

Earlier work [10] had indicated that MSH facilitates synaptic transmission in elements of the diffuse thalamic projection system possibly via modulation of postsynaptic membranes. Moreover, the diffuse thalamic projection system is implicated in the behavioral effects of ACTH/MSH 4–10 by the finding that lesions in the parafascicular nucleus significantly interfere with conditioned avoidance responding and its resistance to extinction. Further, the diffuse thalamic projection system has traditionally been regarded as primary for the maintenance of vigilance and attentional behaviors.

The lowered threshold for cortical activation that would result from a facilitation of synaptic transmission at the level of the diffuse thalamic projection systems could provide the degree of cortical tone necessary for the maintenance of attentional processes in response to environmental demands. The lack of a peptide effect on autonomic parameters such as galvanic skin potential and heart rate would indicate that only the thalamic elements of the reticular activating system are involved and that the observed behaviors are not due to a generalized arousal.

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