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A Comparative Study of the Efficacy of $ACTH_{4-9}$ Analog, Methylphenidate, and Placebo on Attention Deficit Disorder with Hyperkinesis

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The present study compared the behavioral performance of 30 children with attention deficit disorder with hyperkinesis (HK) on electrophysiological, biochemical, behavioral, and psychometric measurements. HK children were partitioned into cells of 10 and were then treated with placebo, methylphenidate, and adrenocorticotropic hormone fractions ($ACTH_{4-9}$ analog), respectively, in a double-blind randomized cell sequence according to body weight. The results revealed that HK children on methylphenidate manifested a significantly greater vasomotor reactivity, behavioral improvement, and learning receptivity than did HK children taking $ACTH_{4-9}$ analog and/or placebo. Future research implications with $ACTH_{4-9}$ and HK children are discussed.

THE BRAIN is known to contain many peptides of diverse molecular weight and complexity. The larger ones contribute to the structure and the enzymatic machinery essential for the metabolism of this complex organ. Smaller ones are hormones and some may be involved in the formation of memory engrams and attentional processes.[1]

It is becoming increasingly apparent that short-chain polypeptides such as melanocyte stimulating hormone and analogues adrenocorticotropic hormone (ACTH) fractions ($ACTH_{4-9}$) influence both behavior and the electrophysiological activity of the brain.[2] More precisely, $ACTH_{4-9}$ analog studies[2-5] have reported enhancement of short-term visual memory, attention, self-rated competence, and observer-rated sociability. These behavioral and neurophysiological findings indicate that ACTH and its fractional analogues have direct, extraadrenal effects on central nervous system functioning.

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Attention deficit disorder with hyperkinesis (HK) is now quite well recognized as a clinical syndrome in children who manifest difficulties in attention, memory, and motivation, with or without hyperactivity.[6] (The term "hyperkinetic syndrome" is used here because it encompasses not only the amount of activity but also other behavioral, physiological, and pharmacological correlates that may differentiate HK children from other children.) Studies[7-9] investigating the management of the disorder have reported that methylphenidate reduces distractibility and impulsivity and improves selective attention in both home and school environments. Consequently, methylphenidate has become the usual chemotherapeutic strategy for children with this syndrome.

Recently, Tiwary and co-workers[10] found that two hyperkinetic children who were previously poor responders to methylphenidate exhibited improvement in all aspects of their HK behavior when injected with 0.2 mg of the tripeptide thyrotropin-releasing hormone. $ACTH_{4-9}$, on the other hand, has been reported by Ferris[11] and Willner[12] to improve social competence and friendliness in the elderly. A similar improvement in social behavior was reported in mentally retarded adults by Sandman and colleagues.[13] These improvements occurred at subchronic doses ranging from 5 to 20 mg daily.

The objectives of the present investigation were (1) to compare $ACTH_{4-9}$ with placebo to determine whether or not the peptide improves measurements of attention and behavior in hyperactive children, and (2) to compare methylphenidate to $ACTH_{4-9}$ and placebo to establish the sensitivity of the method to standard therapy.

Materials and Method

This was a double-blind efficacy study comparing three groups of 10 boys, each group receiving a different drug over a 1-week period. Dosage was adjusted for body

TABLE 1. Dosage for 30 children with attention deficit disorder with hyperkinesis, who were grouped according to weight

	Weight groups		
	A	B	C
Weight ranges (kg)	16–25	26–35	36–45
No. of subjects	10	13	7
Fixed doses of drug (mg)	10	15	20
Dose ranges (mg/kg)	0.62–0.40	0.57–0.43	0.56–0.44

weight as illustrated in Table 1. The weight of the subjects ranged from 15 to 50 kg and was within the expected limits for this age group. The desired dose of both active drugs to be administered was 0.5 mg/kg, and this was achieved within 0.1 mg/kg.[14] Medication was dispensed in a single capsule and ingested in the morning. The dosage of 0.5 mg/kg was arrived at in order to allow adjustment for body weight for the reported effective adult dose, ranging from 5 to 20 mg. This regimen had been observed to produce behavioral changes in the elderly and mentally retarded adults after 5 days of administration in single and twice daily administration. The same dosage range is compatible with what is generally being used for methylphenidate. The three different treatments were stratified within each "weight group" so that nearly equal drug treatment groups could be obtained for each weight group.

Thirty children were included in the study. They were all male, aged 6 to 12 years, and had a clinical diagnosis of attention deficit disorder with hyperkinesis.

For inclusion, the hyperkinesis rating required a score of 15 or more on the Conners' Short Form Rating Scale[15] and hyperkinetic behavior had to be apparent throughout most of the day. The untreated behavior had to be a cause of severe difficulty both at home and at school. All children with an intelligence quotient (Wechsler Intelligence Scale for Children) of 85 or less and/or abnormal perceptual functioning were excluded.

The 7-day drug-free period was followed by a week of placebo treatment. After the placebo washout, treatment was assigned in a double-blind and random manner to either ACTH$_{4-9}$, methylphenidate, or placebo.

Visual, auditory, and tactile screening assessments were made during the drug-free period.

Informed signed consent was obtained from both parents and/or legal guardians of each child. A familiarization session with the testing procedure was held prior to the placebo washout.

The parents or guardians were instructed to administer the experimental medication each morning at 7:30 a.m. on the days of assessment. The medication was administered 90 min prior to the testing session, which was held at the same time for each child on each occasion. These testing sessions were at the end of the placebo week and after a week of double-blind medication administration. In each of the two testing sessions each child did the same tests with the same assessor. The total testing time including breakfast averaged 120 min and ranged from 90 to 135 min.

Psychophysiological assessment

Skin conductance and finger pulse amplitude. The children were seated in a sound-attenuated room with controlled temperature and humidity. The electrodermal activity was recorded on a Beckman 611 dymograph at a paper speed of 5 mm/sec. Skin conductance was recorded as a direct current phenomenon via Beckman silver-silver chloride electrodes, filled with Beckman sodium chloride paste and taped to the terminal phalanx of the first and third fingers of the dominant hand.

Finger pulse amplitude was recorded with a Beckman photoplethysmograph from the first phalanx of the second finger of the nondominant hand. Pulse amplitude measures were employed to a time constant of 0.03 sec.

Reaction time. The reaction time apparatus was triggered by preprogrammed auditory and visual stimuli presentations. The first tone acted as a warning signal. This was a 500-Hz tone of 70-dB intensity and of 1-sec duration. Onset of the warning signal marked the beginning of a 10-sec preparatory interval, at the end of which another tone activated the reaction signal. This consisted of a protected 7.5 watt light bulb located, along with the response button, on the right arm of the subject's chair. Trials were separated by a 50-sec interval. The circuit was constructed so that the reaction signal would not appear unless the response button was depressed. The reaction time was thus measured using an electric clock timer. The onset and termination of the warning and reaction signals and the subjects' responses were automatically recorded on the polygraph chart record.

Psychometric assessment

Conners' Short Form Rating Scale (CSS). Conners[16] shortened his original 39-item rating scale to 10 items. Conners and colleagues[15] were able to differentiate between hyperactive subjects receiving dextroamphetamine, magnesium pemoline, and placebo with this scale. Sprague and Sleator[17] found the CSS sensitive enough to pick up dosage effects in a study using methylphenidate with hyperactive children. In the present study the CSS, which is scored on a four-point (0–3) scale, was completed by both parents and clinicians. The score for a child is the sum over the 10 items.

Conners' Rating Scale. Conners[16] has developed a widely used rating scale for teachers. That scale was factor analyzed to give five factors: (1) hyperactivity, (2) conduct-problem, (3) inattentive-passive, (4) tension-anxiety, and (5) sociability. The score for each factor is

based upon the mean of the items within the factor; a four-point scale (0–3) is used. The teachers were asked to rate the classroom behavior of the HK children during the placebo and active drug phase of the study.

Matching Familiar Figures Test (MFF). The children's form of the MFF consists of 12 standard pictures familiar to children and six variants of each standard. The subject is required to point to that variant which is identical to the standard, which remains in view. Two scores are thus obtained for each subject: (1) the mean latency to the first response on each of the 12 items, and (2) the total number of errors on each item.

Campbell and associates[18] have reported that hyperactive subjects receive higher impulsivity scores than normal subjects on this test and that methylphenidate significantly improved the performance of the hyperactive subjects on both the latency and error measures.

Memory for Design Test. In this test, which assesses attention and visual memory, a series of 15 designs for 5 sec are presented and then each child was asked to draw them from memory. The test takes 10 min to administer. The same set of designs was always used on the first (pretreatment).

Physical assessment

At the end of the drug-free period, each subject underwent a physical assessment of hematological and biochemical functions. This included a complete blood count, urinalysis, and liver and kidney function tests. Blood pressure and pulse were recorded and a standard 16-channel clinical electroencephalogram was done. These same procedures were repeated after the double-blind treatment period. The electroencephalogram was interpreted by a neurologist who was blind to drug conditions.

Data quantification

Table 2 illustrates the type and procedure of quantification used for each index in the current study. In order to explore the preresidual and postresidual drug change, the BMPD-P2V program was used.[19]

Results

The results of the current study were explored as separate sets. The following sets were analyzed: psychophysiological, psychometric, and clinical. The autonomic psychophysiological set consisted of digital blood flow and skin conductance being measured at the beginning and at the end of the testing session. The mean reaction time, memory for design test errors, MFF latency errors, and the number of correct responses on the first trial made up the psychometric set. The clinical set was composed of the Conners' hyperkinesis index and the teachers' rating scale scores.

Tables 3 to 5 illustrate the results obtained comparing the three treatment groups on each of the dependent variables. Only the digital blood flow measured at the end of the experimental session and the Conners' HK index were significantly different on the predrug and postdrug comparisons. HK children treated with methylphenidate had a significant lower digital blood flow and hyperactivity index after 1 week of drug administration than HK children on placebo and $ACTH_{4-9}$ analog. Although not illustrated in Tables 3 to 5, there were no drug-weight group interactions.

Electroencephalogram, hematology, blood chemistry, and urinalysis were within normal limits prior to treatment and remained so after treatment for all three weight and drug groups.

TABLE 2. Summary description of $ACTH_{4-9}$-dependent variables

System	Index	Quantification
Psychometric	Memory for design	msec
	Matching familiar figures:	
	Latency	sec
	Errors	errors
	Reaction time	msec
	Mean reaction time	msec
Clinical	Conners' rating	0–30 points
	Conners' teacher	0–50 points
Psychophysiology	Digital pulse volume (DPV) (individual range corrections): $\phi_{ix} = \frac{DPV_{ix} - DPV_{i(min)}}{DPV_{i(max)} - SE_{i(min)}}$	Mean number of mm over a period of every 10 sec during 10-min relaxation
	Skin conductance (SC) (individual range corrections): $\phi = \frac{SC_{ix} - SC_{i(min)}}{SC_{i(max)} - SC_{i(min)}}$	Mean SC level in mho every 10 sec during 10-min relaxation

TABLE 3. Mean electrodermal activity and digital blood flow

Variable	Placebo	Before methylphenidate	ACTH$_{4-9}$	Placebo	After methylphenidate	ACTH$_{4-9}$	F^a	p
Digital blood flow (mm)								
Beginning	85.5 (9.4)[b]	85.6 (14.4)	85.6 (18.1)	78.8 (6.7)	94.4 (11.0)	81.4 (13.4)	0.29	0.74
End	95.2 (8.2)	91.4 (11.5)	81.0 (18.1)	85.0 (7.1)	79.3 (23.6)[c]	85.9 (12.4)	3.62	0.02[d]
Skin conductance (mho)								
Beginning	9.2 (2.3)	5.2 (3.8)	6.3 (2.9)	9.1 (2.9)	7.4 (5.7)	9.2 (3.5)	0.10	0.98
End	9.2 (2.4)	6.3 (4.8)	6.2 (3.4)	9.3 (3.1)	7.6 (5.4)	8.9 (3.9)	9.11	0.97

[a] F values of weight-drug groups repeated.
[b] Numbers in parentheses are standard deviations.
[c] The high standard deviation is attributable to one subject having a grossly deviant reading.
[d] Significant between methylphenidate pre-treatment and posttreatment.

TABLE 4. Psychometric testing with the Memory for Design Test (MFD) and the Matching Familiar Figures Test (MFF) before and after treatment

Variable	Placebo	Before methylphenidate	ACTH$_{4-9}$	Placebo	After methylphenidate	ACTH$_{4-9}$	F^a	p
MFD	2.1 (1.5)[b]	4.9 (2.7)	2.7 (2.5)	1.9 (1.8)	4.7 (2.4)	2.53 (2.81)	0.39	0.81
MFF latency (sec)	7.3 (2.2)	8.1 (2.9)	8.6 (3.7)	11.6 (5.3)	8.2 (3.7)	7.9 (4.6)	0.61	0.65
MFF errors	6.8 (2.0)	7.8 (3.0)	8.2 (2.5)	4.8 (2.2)	7.5 (2.2)	8.3 (3.5)	0.08	0.98
MFF first trial (sec)	2.6 (0.23)	2.3 (1.5)	2.5 (1.03)	3.0 (1.0)	2.2 (0.56)	2.3 (0.78)	0.14	0.96
Mean reaction time (m/sec)	0.52 (0.2)	0.59 (0.0)	0.80 (0.4)	0.51 (0.2)	0.59 (0.1)	0.82 (0.4)	0.76	0.56

[a] F values of weight-drug groups repeated.
[b] Numbers in parentheses are standard deviations.

TABLE 5. Conners' rating scales

Variable	Placebo	Before methylphenidate	ACTH$_{4-9}$	Placebo	After methylphenidate	ACTH$_{4-9}$	F^a	p
Conners' Short Form Rating Scale (0–30 points)	17.7 (3.7)[b]	17.0 (6.3)	21.7 (4.0)	16.4 (3.8)	8.4 (6.6)	16.7 (5.2)	8.10	0.009[c]
Conners' Rating Scale (0–50 points)	42.7 (14.2)	41.4 (18.3)	39.1 (17.1)	46.1 (20.6)	30.47 (17.3)	37.3 (14.7)	0.46	0.76

[a] F values of weight-drug groups repeated.
[b] Numbers in parentheses are standard deviations.
[c] Significant between methylphenidate pretreatment and posttreatment.

Discussion

The primary purpose of the present investigation was to compare three groups of HK children on placebo, methylphenidate, and ACTH$_{4-9}$ in a randomized group design. This is the first reported attempt at clarifying the effect of ACTH$_{4-9}$ on behavioral, psychometric, and autonomic characteristics of hyperkinetic children. Although dosage was adjusted for weight to reflect reported effective adult dosage, this did not appear to be a significant factor in the treatment of these children.

Despite the limitations of the sample size, short time exposure, and difficulties of available psychometric instruments, these results suggest that methylphenidate produces a significantly higher pulse rate and lower skin conductance in comparison to ACTH$_{4-9}$ and/or placebo. This is consistent with earlier reported findings on methylphenidate efficacy.[20]

Although a short-term screening study such as this one with ACTH$_{4-9}$ analog does allow one to speculate that longer administration may secondarily produce improved attentional performance, the present findings do not support this at the moment.

However, an interesting observation made by the parents of three HK children on ACTH$_{4-9}$ was that their children were more sociable while on the peptide. That observation was supported by a reduction in the Conners' HK index as rated by the teachers. That is, these children were more sociable and presented fewer conduct problems such as unnecessary attention-seeking and hyperactivity both at school and at home. The improvement in sociability was not accompanied by changes in mood of a dysphoric nature as was reported by Rapoport and co-workers[21] for d-amphetamine and methylphenidate. Nevertheless, the increase in sociability and reduced hyperactivity seem consistent with a previous report on ACTH$_{4-10}$.[22]

Additionally, no physical and/or psychological side effects were reported and observed by any HK child while on ACTH$_{4-9}$ analog. On the other hand, HK chil-

dren who were on methylphenidate reported the usual side effects such as diminished appetite and difficulties in falling asleep.

The implications of these findings for future studies with $ACTH_{4-9}$ analog suggest that single case studies[23] with a time-series orientation[24] may be more specific in detecting treatment effect. Such designs would permit a staircase increase of dosage levels over time and may thus confirm the therapeutic trends observed in these findings for other subgroups of hyperkinetics as well as for children and adults[25] who manifest an attention deficit.

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