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Disregulation of Hypothalamic-Pituitary-Adrenal Axis in the Mentally Retarded

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SANDMAN, C. A., J. L. BARRON AND L. PARKER. *Disregulation of hypothalamic-pituitary-adrenal axis in the mentally retarded*. PHARMACOL BIOCHEM BEHAV 23(1) 21-26, 1985.—Previous reports of cognitive and social improvement in the mentally retarded after administration of MSH/ACTH fragments suggested disregulation of the hypothalamic-pituitary-adrenal (HPA) axis. The current study examined the integrity of this system with the Dexamethasone Suppression Test (DST). The DST is a biological index of HPA integrity and recently has been used as a diagnostic aid for endogenous depression. Thirty-five mentally retarded patients were administered 1 mg of dexamethasone just after a sample of blood was taken. Blood samples were analyzed for cortisol by RIA at 11:00 p.m. (basal), 8:00 a.m., 4:00 p.m., and 10:00 p.m. Between 40% and 48% (depending on sampling) of the patients failed to suppress cortisol ($>4 \mu\text{g/dl}$), after the DST challenge. The results suggested that a significant proportion of mentally retarded patients have a DST index reflecting a disordered HPA axis and complements earlier studies of cognitive enhancement observed after treatment with MSH/ACTH fragments. The possibility that the stress of hospitalization was related to a disordered HPA was suggested. The possible co-existence of depression in the mentally retarded invites further study.

Dexamethasone suppression test (DST)	Hypothalamic-pituitary-adrenal (HPA) axis	MSH/ACTH fragments
Mentally retarded	Depression	Stress

PREVIOUS reports from our laboratory [18, 21, 26] indicated that MSH/ACTH fragments effectively, but transiently, improved the cognitive and social functioning of heterogeneous groups of mentally retarded patients. These results were consistent with a large body of animal literature [4, 5, 16, 17, 18, 24] and with studies in healthy volunteers [8, 10, 13, 15, 17, 25, 27]. However, the effects in retarded patients were more dramatic than in normal groups suggesting disregulation of hypothalamic-pituitary-adrenal (HPA) axis. Dynamic function tests of neurochemical systems, by challenge with pharmacological probes, have been useful diagnostic aids in patients with depression [2,3] and in the mentally retarded [1].

The most widely used challenge of the HPA axis is the dexamethasone suppression test (DST). The DST is an episode-related biological test used for diagnosis of neuroendocrine abnormalities (e.g., Cushing's Syndrome) and more recently for endogenous depression. The diagnostic per-

formance of the DST is evaluated with the calculations of specificity, sensitivity and diagnostic confidence. The overall specificity of the DST (the proportion of non-endogenously depressed patients in whom normal results are observed) ranges from 86 to 96%, while the sensitivity of the DST (e.g., the proportion of endogenously depressed patients in whom abnormal results are observed) ranges from 43 to 69% [2]. Overall, the diagnostic confidence (the proportion of abnormal test results that were true positive for endogenous depression) ranges from 83 to 95% depending upon the plasma cortisol criterion value used [3]. Thus, even though a positive test is a useful index of endogenous depression, a negative test does not necessarily rule it out.

In the present context, evaluation of the DST not only may provide useful information regarding depression but also the dynamic response of the HPA in the retarded. The present study was conducted to assess the response to the overnight DST as an index of the HPA in mentally retarded

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TABLE 1

DEMOGRAPHIC VARIABLES OF MENTALLY RETARDED PATIENTS
IN DST STUDY

Variable	Mean	Standard Deviation
Age (in years)	30.43	7.63
Length of Institutionalization (in months)	233.16	99.36
Mental Age (in months)	50.92	31.23
Social Age (in months)	57.11	37.23
Level of Retardation (%)		
Profound	41%	
Severe	25%	
Moderate	22%	
Mild	12%	

N=35 (19 Males: 16 Females).

individuals. In subgroups of clients, the level of plasma cortisol was correlated with dosage of sedative/hypnotics and anticonvulsants. Finally, multivariate predictors of DST response were generated by discriminant function analysis.

METHOD

Subjects

Written consent of parents or legal guardians was obtained for thirty-five mentally retarded patients (19 male and 16 females) from the Adolescent Development and Habilitation Programs at Fairview Developmental Community. Complete data were available for 28 patients. Patients ranged in age from 17 years to 45 years with a mean age ($\pm$ SD) of 30.41 ± 7.63 years. Patients' length of institutionalization ranged from 4 years to 39 years with a mean ($\pm$ SD) of 19.32 ± 8.27 years.

The most frequent medical diagnoses among these patients were mental retardation associated with or due to: unknown prenatal influence, other, defective fetal development (20 percent); unknown prenatal influence, other, unspecified (17 percent); disorders of metabolism or nutrition, amino acid disorders, Phenylketonuria (11 percent); unknown prenatal influence, cerebral malformation, not further specified (9 percent); and trauma or physical agent, perinatal hypoxia (6 percent). The mental ages ranged from 14 to 129 months with a mean ($\pm$ SD) of 50.92 ± 31.23 months. Social ages ranged from 20 to 139 months with a mean ($\pm$ SD) of 57.11 ± 37.42 months. Overall, the population consisted of 41 percent profoundly retarded (IQ below 20), 25 percent severely retarded (IQ 20 to 34), 22 percent moderately retarded (IQ 35 to 49), and 12 percent mildly retarded patients (IQ 50 to 70; Table 1).

Patients were excluded from this study if they manifested kidney or liver dysfunction (BUN, creatine, SGOT or SGPT, Bilirubin and ALK Phos were all normal), severe anemia, diabetes mellitus, Cushing's disease or syndrome (blood pressure $>160/90$, high glucose, and high potassium), Addison's disease (high potassium and sodium), pregnancy, severe weight loss, obesity or major physical illness, e.g., stable organized brain disease. Although 11 of the patients

TABLE 2

DEMOGRAPHIC AND DESCRIPTIVE VARIABLES COLLECTED FOR
EACH PATIENT IN THE DST STUDY

1. Sex
2. Height
3. Weight
4. Age
5. Length of Hospitalization
6. Prenatal History
7. Birth Trauma
8. A.A.M.D. Diagnosis
9. Presence of Physical Handicap
10. Presence of Sensory Handicap
11. Presence of Dysmenorrhea (if female)
12. Mental Age
13. Social Age
14. E.E.G. Report
15. Paradoxical Response to Medication
16. Medical Orders for Sedative-Hypnotics (phenobarbital)
17. Medical Orders for Anticonvulsants
18. Medical Orders for Antipsychotics
19. Medical Orders for Lithium
20. SMA 20 Levels
21. Family History of Mental Illness or Mental Retardation
22. Maternal Miscarriage prior to Patient's Birth
23. Staff Identified as Depressed
24. Staff Identified as Exhibiting Cyclic Mood Swings
25. Harmful to Self
26. Harmful to Others
27. Inappropriate Activity Level
28. Stereotypy

received anticonvulsant regimes for seizure disorders, none received ACTH, corticosteroid or thyroid therapy, reserpine, narcotic agents, high-dose benzodiazepines, or hormonal preparations, e.g., birth control pills.

Procedure

Dexamethasone Suppression Test (DST). The overnight DST procedure was used in this study. This test involved drawing 10 ml blood by venipuncture between 10:30 and 11:30 p.m. and oral administration of 1 mg of the glucocorticoid, dexamethasone, followed by 10 ml blood samples at 8:00 a.m., 4:00 p.m., and 10:00 p.m. the following day. Serum was separated by centrifugation immediately after withdrawal and frozen until assayed. Plasma cortisol concentrations were evaluated from the coded blood samples taken.

Plasma cortisol levels were determined by radioimmunoassay (RIA). This procedure involved extracting serum into 15 volumes of diethyl ether, using a tritiated label from the New England Nuclear Corporation (Boston, MA) purified by Florisil column chromatography. Antiserum was made in New Zealand rabbits immunized against the conjugate 4-pregnen-11, 17, 21-tiol-3, 20-dione 21-hemisuccinate BSA, obtained from Steraloids (Q 3910; Wilton, NH). Cross-reactions for the cortisol antiserum are as follows: 11-deoxycortisol 16%; 17-OH progesterone 14%; cortisone 6%; corticosterone, DOC and progesterone $<0.1\%$; and pregnenolone, 17-OH pregnenolone, testosterone, DHA, and androstenedione $<0.01\%$. Bound and free steroid labels were separated by a 1:10 mixture of dextran (Schwartz-Mann, Inc., Orangeburg, NY) and charcoal (MCB, Inc., Norwood, OH). Assay sensitivity was 29 pg per tube. All

samples were analyzed in the same assay run. Intra-assay variation was 4.2%.

Patients were classified as non-suppressors if any of the three post-Dexamethasone plasma cortisol concentrations were greater than 4 $\mu\text{g/dl}$. Even though 5 $\mu\text{g/dl}$ often is used as the most conservative criterion for judging an abnormal DST result, there is relatively little loss of diagnostic performance when the criterion value is lowered to 4 $\mu\text{g/dl}$ [2]. Demographic and descriptive information was obtained for each subject on a survey data sheet which consisted of twenty-eight items (Table 2).

RESULTS

Fifteen of the 28 subjects (54%) escaped suppression after challenge with 1 mg of dexamethasone. However some of the patients received medication which might contaminate the DST results. Thus, before extensive analysis of the data were conducted, analyses of drug effects were computed.

Cortisol Levels and Anticonvulsants

Since there is correlational evidence that phenytoin and phenobarbital may invalidate the DST results, data were analyzed separately from patients receiving these medications. Eight patients received only phenobarbital and 3 received both phenobarbital and phenytoin. No patients in this study received only phenytoin. The dosage of phenobarbital for these 11 patients were correlated with plasma cortisol levels for the four test periods. The data are displayed in Figs. 1A–1D.

The relationship between cortisol and dosage of phenobarbital approaches significance only when the patients receiving phenytoin are included, especially for the 4:00 p.m. and 10:00 p.m. samples. However, exclusion of the subjects receiving phenytoin yields dramatically different results. The correlations between cortisol and dose in these eight patients approaches zero.

Inspection of Fig. 1 indicates that 50% to 63% of the patients have cortisol levels elevated above 4 $\mu\text{g/dl}$ compared to 40% to 48% of the drug-free patients (depending upon the times sampled). Thus, although more patients receiving phenobarbital in any dose have a slightly greater likelihood of elevated cortisol, the difference from patients not receiving phenobarbital is not compelling. The three patients receiving phenytoin were not included in subsequent analyses.

Suppression Versus Nonsuppression

In order to determine if escape from suppression was predictable heuristic linear equations were constructed from stepwise discriminant function analysis (SDFA) using the variables in Table 2. The analysis were done separately for basal, the 8:00 a.m.–4:00 p.m., and the 4:00 p.m.–10:00 p.m. blood samples. In order to increase sensitivity adjacent samples were grouped [3].

Basal levels. Two separate groups were constructed based upon basal cortisol levels using 4 $\mu\text{g/dl}$ as the criterion. Nearly perfect separation of groups based upon the pre-DST tests was determined. High basal levels of cortisol were related significantly to six of the dependent variables: greater likelihood of prenatal trauma; likelihood of receiving antipsychotic medication, being female, higher mental age, and increased stereotypy. However, pertinent to the current study there was virtually no relationship between basal cortisol level and post-DST cortisol findings (see Table 3).

FIG. 1. Scatter plot distribution of dose of phenobarbital with plasma cortisol level for 10 p.m. basal (A); 8 a.m. post-dex (B); 4 p.m. post-dex (C) and 10 p.m. post-dex (D). Plasma cortisol levels $\times 10$ (○ phenobarbital; ● phenobarbital + phenytoin).

TABLE 3
CORRELATIONS AMONG PLASMA CORTISOL AT FOUR DIFFERENT TEST PERIODS AFTER DST

Cortisol	8:00 a.m. Plasma Cortisol	4:00 p.m. Plasma Cortisol	10:00 p.m. Plasma
Basal Plasma Cortisol	.28	.24	.46
8:00 a.m. Plasma Cortisol		.81	.43
4:00 p.m. Plasma Cortisol			.33

8:00 a.m.–4:00 p.m. samples. Based upon cortisol levels, three groups were constructed. One group consisted of patients with plasma cortisol levels above 4 $\mu\text{g/dl}$ at both 8:00 a.m. and 4:00 p.m. (N=5). The second group had elevated cortisol either at 8:00 a.m. or 4:00 p.m. (N=5). The third group had cortisol levels below criterion for both samples (N=15). Highly significant differences among these three groups were evident with this exploratory analysis. The separation based upon canonical variables is illustrated in Fig. 2A. The combination of variables in this statistically significant separation ($F(10,36)=8.44$, $p<0.001$; first 5 steps) is presented in Table 4A.

The three groups have very different profiles. The group with normal cortisol levels during both sampling epochs is noticeably different from the non-suppressors by the higher social age and longer hospitalization. Compared with the group with both samples elevated, the group with only one

FIG. 2. Separation of groups by linear combination of variables in stepwise discriminant analysis. Panel A presents data for 8 a.m. and 4 p.m. Panel B presents data for 4 p.m. and 10 p.m.

sample above criterion had fewer cyclic mood swings, a normal EEG, lower social age and shorter hospitalization.

4:00 p.m.-10:00 p.m. samples. Three groups also were constructed for the 4:00 p.m. and 10:00 p.m. samples consisting of patients with cortisol levels elevated during both sampling epochs ($N=2$), only one period ($N=10$), or neither ($N=13$). The spatial separation of these groups is illustrated in Fig. 2B. The results of the SDFA must be considered tentative because of the inadmissibly small sample size in the sustainers. The first 5 variables to enter the equation which significantly, $F(10,36)=5.41$, $p<0.01$, differentiated these groups are presented in Table 4B. As with the previous analysis, the samples of the "sustained" non-suppressors and the escapers were most similar. One interesting finding emerging from a contrast of the two analyses, was that sedatives influenced the 8:00 a.m. DST findings more than the 4:00 p.m. and 10:00 p.m. samples. However, "sustained" non-suppressors in each analyses were more likely to receive a sedative.

DISCUSSION

Depending upon sampling period, 40% go 48% of mentally retarded patients had a dysregulated HPA response. The unusually high incidence of escape from suppression in a heterogeneous sample of mentally retarded patients complements the improvement in cognitive and social skills, after treatment with MSH/ACTH fragments [18, 21, 26]. If administration of peptides to retarded patients is effective because they prime or stimulate a disordered or subsensitive system, then the DST results may be used as a guide for predicting positive response to peptides.

TABLE 4
VARIABLES CONTRIBUTING TO THE SEPARATION OF GROUPS AT THE 8:00 A.M. AND 4:00 P.M. AND 4:00 AND 10:00 P.M. SAMPLES

	A		
	Periods with Elevated Cortisol		
	8 a.m. or 4 p.m. (N=5)	8 a.m. and 4 p.m. (N=5)	Neither (N=5)
Classification Accuracy with Jackknifing Procedures	100%	80%	80%
Variables			
Sedative/Hypnotics (phenobarbital)	Increased	Increased	Decreased
Cyclic Mood Swings	Decreased	Increased	Increased
EEG	Normal	Abnormal	Abnormal
Social Age	39 months	53 months	69 months
Length of Hospitalization	142 months	186 months	246 months
	B		
	Periods with Elevated Cortisol		
	4 p.m. and 10 p.m. (N=10)	4 p.m. or 10 p.m. (N=2)	Neither (N=13)
Classification Accuracy with Jackknifing Procedures	90%	100%	77%
Variables			
Sedative/Hypnotic	Decreased	Increased	None
Sex	5=F;5=M	Both Female	3=F;10=M
Length of Hospitalization	171 months	248 months	214 months
Mental Age	31 months	70 months	45 months
Cyclic Mood Swings	None	Increased	Increased

Whether a positive DST in these patients is a biological marker of endogenous depression is unknown. There are obstacles which may confound the use of a challenge to the hypothalamic-pituitary-adrenal (HPA) axis in retarded individuals. For instance, it is often difficult to secure drug-free institutionalized mentally retarded clients. Indeed, many of the clients receive anticonvulsants for seizure disorders. It is well documented that some anticonvulsants, e.g., phenytoin (dilantin) and phenobarbital invalidate the DST because they may accelerate hepatic conjugation and biliary excretion of dexamethasone. Phenytoin may increase dexamethasone metabolism by enhancing its conversion to unconjugated metabolites of greater polarity [11]. Similarly, phenobarbital, a sedative-hypnotic medication often prescribed for seizure control, may increase hepatic microsomal enzyme activation [12] and inhibit cortisol metabolism [22]. Thus, the deactivation of synthetic cortisol disinhibits the negative feedback between cortisol and ACTH and results in higher plasma corticosteroid levels. The end result is an appearance of escape from suppression (i.e., a false positive) because the half-life of dexamethasone in plasma is reduced from about 270 minutes to 120 minutes [2]. In the current study, there was no effect of dosage of phenobarbital on plasma cortisol. A second, and not mutually exclusive conclusion, is that phenobarbital may influence cortisol levels independently of dose.

Even though the prevailing view is that psychiatric disorders cannot co-exist with mental retardation, Eaton and Menolascino [7] suggested that retardation may yield greater susceptibility to psychiatric disorders. Sovner and Hurley [23] concluded that developmentally impaired cognitive and social functioning did not preclude the occurrence of affective symptomatology. Since standard DSM III [6] criteria cannot be applied to severely and profoundly retarded patients, it is difficult to assess the validity of the DST as an index of suppression in this group. Further, the specificity of the DST may be compromised in patients with central nervous system dysfunctions [9].

Equations generated with SDFA suggested that the DST

response reflected adaptation to institutionalization. For instance, the group with one blood sample elevated had the shortest hospitalization (Phase 1). This group also had the lowest social and mental age and the greatest reliance on sedative/hypnotic medication but a normal EEG. The group with both plasma cortisol samples elevated (sustainers), may represent Phase 2 of adjustment. This group, with clear signs that a severe breakdown in the HPA system has occurred, had longer hospitalization, continued reliance on sedative/hypnotics, and an abnormal EEG. However, the influence of institutionalization may be reflected as an increase in social and mental age of these patients. Phase 3 may be represented by the group with a "normal" suppressive response. They have the longest hospitalization, highest social functioning but an abnormal EEG, appearance of mood swings and reduced reliance on sedative/hypnotics. Thus, enduring institutionalization may result in management of clients behavior and the development of compliance at the cost of physiological (and perhaps behavioral) plasticity. With time, reliance on sedative/hypnotics was diminished but the neurological and psychiatric scars may remain masked beneath a rehearsed behavioral repertoire. In this context, an abnormal response, escape from suppression, may predict a positive response to intervention (peptide administration).

This is the first report of the DST in mentally retarded individuals. Evidence is presented that a sizeable proportion of mentally retarded persons fail to suppress cortisol when administered dexamethasone. These findings complement earlier results of improved cognitive and social ability after treatment with MSH/ACTH fragments. These data also suggest a biological marker for depression or response to stress in retarded patients.

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