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Research Article

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Auditory Detection and Perception in Normal Man and in Patients with Adrenal Cortical Insufficiency: Effect of Adrenal Cortical Steroids

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ABSTRACT Auditory detection thresholds for sinusoidal tones and various tests of auditory perception were determined in 12 patients with adrenal cortical insufficiency (seven with Addison's disease and five with panhypopituitarism) and compared to those in normal volunteers. In adrenal cortical insufficiency auditory detection sensitivity was significantly more acute than normal, and judgments of loudness and of the contralateral threshold shift were made at levels more than 20 db below those of normal subjects. Thus both the lower and the upper limits of the dynamic auditory range are significantly decreased in these patients. Speech discrimination ability of the patients was significantly impaired as was their difference limens, their alternate binaural loudness balances, and their ability to localize tones in space.

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Treatment with prednisolone or with maintenance doses of carbohydrate-active steroids returned auditory detection and perception to normal in every patient tested.

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The inability of the untreated patients to perform the various auditory perception tasks indicates that they have a defect in their ability to integrate incoming sensory stimuli. This defect may be related to the alteration in the timing of transmission of neural impulses along axons and across synapses which occurs in these patients when their carbohydrate-active steroid is removed. This decreased integrative capacity occurs at the same time that they are able to detect many types of sensory stimuli significantly better than normal subjects. This interrelationship between increased detection sensitivity and decreased perceptual ability is dependent upon the absence of carbohydrate-active steroids, for when these steroids are replaced both detection sensitivity and perceptual ability revert to normal.

INTRODUCTION

It has been shown previously that patients with untreated adrenal cortical insufficiency exhibit markedly increased detection sensitivity for taste, smell, and hearing. Treatment of these patients with deoxycorticosterone acetate (DOCA) for 2-9 days produced no alteration in taste, smell, or hearing thresholds, but treatment with carbohydrate-active steroids for 18-72 hr generally returned taste, smell, and hearing thresholds to normal (1-3). These studies indicated further that changes in extracellular fluid volume could not account for these effects (1-3).

Careful observation of the responses of the pa-

tients with untreated adrenal cortical insufficiency during these experiments suggested that although detection sensitivity for taste and smell was significantly increased in a number of sensory modalities, perceptual ability was decreased. Initial observations suggested that these phenomena also occurred in hearing; e.g., when placed in the sound chamber before auditory testing and deprived of visual and gestural cues patients had difficulty in carrying out instructions given through the earphones.

Because of these observations, it became apparent that patients with untreated adrenal cortical insufficiency experienced difficulty with perception or "integration" of sensory stimuli. The present study was designed to evaluate the manner in which patients with adrenal cortical insufficiency respond to a battery of auditory perceptual tasks and to explore the effect of treatment with adrenal cortical hormones and adrenocorticotropin.

METHODS

The subjects of this study were 20 normal volunteers, aged 18-42, seven patients with adrenal cortical insufficiency, aged 19-57, and five patients with anterior pituitary insufficiency, aged 14-54. All patients with adrenal cortical insufficiency had clinical features of this disease, urinary 17-hydroxycorticosteroid excretion below 2 mg/24 hr, which did not increase with 40 U of adrenocorticotropin (ACTH) given intravenously over 8 hr each day for 4 days (except for V. M. and C. M. whose urinary 17-hydroxycorticosteroids rose to 5.0 and 11.6 mg/24 hr, respectively, on the 4th day of ACTH). All patients with anterior pituitary insufficiency had hypothyroidism, hypogonadism, and adrenal cortical insufficiency, with urinary 17-hydroxycorticosteroids below 2.2 mg/24 hr, rising above 10 mg/24 hr after infusion of 40 U of ACTH given intravenously over 8 hr each day for 2 or more days. Taste, smell, and (or) hearing thresholds have been previously reported for 8 of these 12 patients (1-3). All patients remained on an air-conditioned metabolic ward and ate a regular diet, which was well tolerated even when they were not receiving treatment. Sodium intake was 100-200 mEq/day. Body weight, determined with metabolic scales daily on arising, was used to provide a gross estimate of changes in the volume of body fluids. None of the subjects or patients gave a history of hearing loss or of ear disease. Otolaryngeal examination revealed no gross abnormality in any of the normal subjects or patients with adrenal cortical insufficiency. The patients were studied under five conditions: (a) untreated for 4 or more days, (b) treated with DOCA, 20 mg/day for 3-9 days, (c) treated with prednisolone, 20 mg/day for 2-7 days, (d) treated with 40 U of ACTH intravenously over 8 hr for 5 days, and (e) treated with

maintenance dosages of 9 alpha-fluorohydrocortisone (0.05-0.10 mg/day) and prednisolone (5.0-7.5 mg/day), dexamethasone (0.5 mg/day), or cortisone acetate (37.5 mg/day).

Auditory measurements were obtained by the two experimenters of the study, on separate occasions, in the afternoon hours. One of the experimenters (R.L.D.) participated in the study on a double-blind basis. If, for a given treatment condition, the independent measurements determined by the two experimenters differed by more than 5 db, the data were discarded, and the experiment was repeated.

All auditory measurements were made with the subjects and patients seated alone, comfortably, in an arm chair, in an Industrial Acoustic Corporation 1204 sound chamber. Acoustic signals were provided by a Beltone Model 15C clinical audiometer with a fixed 20 db attenuator in line with the output from the audiometer. The signal was presented separately to the left and right ears of each subject or patient through Telephonics TDH-39 earphones with MX-41/AR cushions. Noise measurements were obtained with the internal sawtooth noise generator of the Beltone audiometer. Speech signals were provided by standard recorded lists of phonetically balanced words (PB) and standard recorded lists of low-pass filtered speech (LPFS); i.e., words from which frequencies above 500 cps had been filtered at a rate of 17 db/octave (4). These recorded lists were played through the audiometer circuit by an Ampex 300 series tape recorder. The speech signals were calibrated with reference to a 1000 cps tone set at 0 intensity on the Volume Unit (VU) meter of the Beltone audiometer. The output of the audiometer was calibrated relative to the International Standards Organization (ISO) standard for hearing thresholds (5).

Auditory detection thresholds for sinusoidal tones over the frequency range of 125-8000 cps were obtained in a standard manner previously described for audiometric thresholds (6). These were obtained by an ascending technic with 5 db intensity increments and a 100% response criterion. Presentation of tones was varied to eliminate order and practice effects. Audiometric thresholds differ in a number of respects from the type of thresholds we reported previously for some of these patients (3). Audiometric thresholds, although not quite as precisely located as the previously reported thresholds, are the most common measurements used for the clinical description of detection sensitivity. The two types of thresholds may be made roughly comparable by appropriate conversion formulas (5). Measurements are expressed in decibel hearing level from the ISO 1964 Standard for hearing thresholds (5); i.e., the attenuator was calibrated such that 0 hearing level corresponded to the standard value for normal hearing, positive values, poorer than normal hearing, and negative values, better than normal hearing. The data presented here are the mean thresholds for the second or better ear tested. Threshold values for normal subjects obtained by this technic are directly comparable to, and in good agreement with, those reported by other investigators (5, 6).

TABLE I
Auditory Detection and Perception Thresholds in 20 Normal Volunteers, Aged 18-42 yr (Mean, 20.7)
and in Patients with Adrenal Cortical Insufficiency, Off Treatment

| Patient | Sex | Age | Weight | Serum Na | Serum K | Loudness judgments | | | | | Speech discrimination | | | | | Contra-lateral threshold shift | Auditory detection threshold | | |
|------------------------------------|-----|-----|--------|----------|---------|--------------------|---------------|---------------------------|--------------------------|---------------|-----------------------|--------------|---------------|------------------|---------------|--------------------------------|------------------------------|---------|----------|
| | | | | | | Mean comfort level | Upper limit | Discomfort level (speech) | Discomfort level (noise) | PB | | LPFS | | Difference limen | db modulation | | db* | 500 cps | 1000 cps |
| | | | | | | | | | | 40 | 60 | 40 | 60 | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| Normal volunteers (mean \pm SEM) | | | | | | | | | | | | | | | | | | | |
| Addison's disease | | | | | | | | | | | | | | | | | | | |
| A. B. | F | 54 | 54.08 | 135 | 5.3 | 45 | 55 | 60 | 45 | 78 | 80 | 12 | 16 | >5.0 | 50 | -5 | -10 | | |
| J. A. E. | F | 33 | 50.83 | 124 | 4.4 | 45 | 57.5 | 65 | 40 | 76 | 74 | 10 | 36 | 4.1 | 40 | -10 | -10 | | |
| V. McC. | M | 52 | 62.18 | 129 | 4.9 | 40 | 55 | 60 | 48 | 88 | 96 | 16 | 36 | 2.4 | 50 | -15 | -15 | | |
| Clar. M. | M | 60 | 72.07 | 126 | 6.0 | 40 | 50 | 60 | 22 | 56 | 96 | 0 | 30 | >5.0 | 40 | +5 | +10 | | |
| P. K. | F | 24 | 46.05 | 137 | 5.1 | 40 | 55 | 67.5 | 54 | 88 | 100 | 10 | 32 | 1.0 | 40 | -10 | -15 | | |
| R. P. | F | 54 | 63.03 | 139 | 3.6 | 40 | 55 | 60 | 45 | 49 | 74 | 0 | 10 | 2.9 | 50 | -15 | -15 | | |
| R. E. | M | 19 | 50.21 | 137 | 4.6 | 10 | 32.5 | 40 | 32 | 62 | 100 | 4 | 24 | 1.3 | 50 | -25 | -20 | | |
| Mean \pm SEM | | | | | | 37 \pm 4.6 | 51 \pm 3.3 | 59 \pm 3.3 | 41 \pm 4.1 | 71 \pm 5.9 | 89 \pm 4.6 | 7 \pm 2.3 | 26 \pm 3.8 | 3.1 \pm 0.6 | 46 \pm 2.0 | -11 \pm 3.6 | -11 \pm 3.7 | | |
| Panhypopituitarism | | | | | | | | | | | | | | | | | | | |
| E. B. | M | 57 | 65.03 | 133 | 4.1 | 35 | 50 | 60 | | 32 | 76 | 0 | 12 | 1.2 | 50 | -15 | -20 | | |
| E. N. | M | 14 | 28.93 | 136 | 4.5 | 40 | 55 | 65 | 44 | 78 | 96 | 6 | 20 | >5.0 | 45 | -15 | -15 | | |
| L. D. | M | 20 | 43.95 | 138 | 5.1 | 55 | 65 | 70 | | 42 | 88 | 12 | 20 | 1.2 | 95 | -5 | -5 | | |
| H. R. | M | 18 | 38.00 | 138 | 5.0 | 35 | 54 | 47.5 | 24 | 54 | 78 | 4 | 24 | >5.0 | 50 | -15 | -20 | | |
| Clau. M. | M | 18 | 31.97 | 135 | 4.4 | 40 | 55 | 60 | 53 | 58 | 92 | 4 | 20 | >5.0 | 50 | -20 | -20 | | |
| Mean \pm SEM | | | | | | 41 \pm 3.0 | 53 \pm 3.3 | 60.5 \pm 3.1 | 40 \pm 4.9 | 53 \pm 6.4 | 86 \pm 3.2 | 5 \pm 1.6 | 19 \pm 1.6 | 3.5 \pm 0.8 | 58 \pm 7.6 | -14 \pm 2.0 | -16 \pm 2.4 | | |
| Total Mean \pm SEM | | | | | | 39 \pm 3.0† | 52 \pm 2.4‡ | 60 \pm 2.4‡ | 41 \pm 3.5‡ | 63 \pm 5.2‡ | 88 \pm 2.8§ | 6 \pm 1.6‡ | 23 \pm 2.5‡ | 3.3 \pm 0.5‡ | 51 \pm 4.2‡ | -12 \pm 2.5‡ | -13 \pm 2.5‡ | | |

pb, phonetically balanced; LPFS, low-pass filtered speech.

* db hearing level from International Standards Organization (ISO) 1964 Standard.

† $P < 0.01$ with respect to results of normal volunteers or to results after treatment with carbohydrate-active steroids.

‡ $P < 0.01$ with respect to results of normal volunteers; § $P < 0.02$ with respect to results after treatment with carbohydrate-active steroids.

TABLE II
Auditory Detection and Perception Thresholds in Adrenal

| Patients | Sex | Age | Weight | Serum Na | Serum K | Loudness judgments | | | |
|-------------------|-----|-----------|-----------|------------------|---------|--------------------|---------------------------|----------------------------|---------------------------|
| | | | | | | Mean comfort level | Upper limit comfort level | Discom-fort level (speech) | Discom-fort level (noise) |
| | | <i>yr</i> | <i>kg</i> | <i>mEq/liter</i> | | | | <i>db*</i> | |
| Addison's disease | | | | | | | | | |
| A. B. | F | 54 | 56.31 | 146 | 3.6 | 45 | 55 | 60 | 47.5 |
| J. A. E. | F | 33 | 52.15 | 137 | 3.9 | 52.5 | 62 | 67.5 | 48 |
| V. McC. | M | 52 | 62.99 | 136 | 5.0 | 50 | 60 | 70 | 52 |
| Clar. M. | M | 60 | 74.04 | 125 | 4.5 | 55 | 60 | 65 | 39 |
| P. K. | F | 24 | 51.63 | 141 | 2.5 | 42.5 | 60 | 65 | 45 |
| R. P. | F | 54 | 62.97 | 137 | 2.8 | 27.5 | 51 | 62.5 | 60 |
| R. E. | M | 19 | 50.67 | 137 | 4.1 | 10 | 30 | 35 | 30 |
| Mean \pm SEM | | | | | | 40 \pm 6.1 ‡ | 54 \pm 4.4 ‡ | 61 \pm 4.4 ‡ | 46 \pm 3.6 ‡ |

PB, phonetically balanced; LPFS, low-pass filtered speech.

* db hearing level from International Standards Organization (ISO) 1964 Standard.

† $P < 0.01$ with respect to results of normal volunteers or to results after treatment with carbohydrate-active steroids.

§ $P < 0.01$ with respect to results of normal volunteers; $P < 0.05$ with respect to results after treatment with carbohydrate-active steroids.

Only values for 500 and 1000 cps will be presented since these were the frequencies to which the perceptual measurements were referenced.

Loudness judgments were obtained by determining various comfort and discomfort levels for speech and noise by standard techniques previously described (6, 7). The mean comfort level for speech (MCLS) is defined as the mean loudness level of conversational speech that the subject appreciates as comfortable. This was determined as follows. The speech circuit of the Beltone audiometer was calibrated to 0 on the VU meter with respect to the conversational live speech level of the investigator. Using this speech, the investigator instructed the subject to signal when the words heard through the earphones were comfortably loud. Speech was presented in ascending intensity from barely detectable to uncomfortable levels at 5-db intervals. If there was a range of loudness within which different intensities seemed equally preferable, the mean of the range was taken as the comfort level. The upper limit of the comfort level for speech (ULCLS) was defined as that sound level at which the subject reported the speech of the investigator to be loud, but not uncomfortable. The discomfort level for speech (DLS) was defined as the sound level at which the subject first reported discomfort with the speech of the investigator. The discomfort level for noise (DLN) was defined as the sound level at which the subject first reported discomfort to the sawtooth noise stimulus from the Beltone audiometer. Each of these four measurements was repeated three times for each subject and for each ear tested. The mean of these three determinations for the second or better ear is reported. Each subject was briefly trained before the testing in order to acquaint him with the test procedure. A range of intensities was explored,

and the subject was questioned as to the loudness characteristics of the sound stimuli.

Speech discrimination measurements were obtained at hearing levels 40 and 60 db above each subject's auditory detection threshold at 1000 cps. Standard phonetically balanced lists of 50 words each (filtered and nonfiltered) were presented to each subject in a standard manner (4, 6). The subject was required to repeat the stimulus word, and his response was recorded. Results are reported in per cent of correct responses at 40 and 60 db above 1000 cps threshold (PB 40 and PB 60, respectively for the nonfiltered words; LPFS 40 and LPFS 60 for the filtered words). Before the presentation of the filtered words a 50 word practice list was presented to each subject 40 and 60 db above threshold in order to familiarize him with the nature of the test stimuli.

A difference limen for intensity (8, 9) was obtained with a 500 cps amplitude modulated (warbling) tone, presented at a level 20 db above each subject's auditory detection threshold at that frequency. The test tone was calibrated on an oscilloscope in decibels of modulation. Modulation was determined from the formula $\log_{10} \Delta I/I$, in which ΔI represents a change in intensity, and I is the reference intensity. For the test, the tone was varied between 0 and 5 db modulation. The subject was required to signal when he first perceived a transition from a steady to a warbling or from a warbling to a steady tone. Each transition was measured three times in each direction for each ear, and the mean of the three measurements for the second ear tested was taken as the difference limen. The data are reported in decibels of modulation.

The contralateral threshold shift (CTS) was determined by a variation of a technic used in a number of

| Speech discrimination | | | | Difference limen | Contra- lateral threshold shift | Auditory detection threshold | |
|-----------------------|---------|--------|---------|---------------------|--|---------------------------------|----------|
| PB | | LPFS | | | | 500 cps | 1000 cps |
| 40 | 60 | 40 | 60 | | | | |
| % correct | | | | db modu- lation | db* | db* | |
| 72 | 86 | 6 | 22 | >5.0 | 45 | -5 | -10 |
| 72 | 88 | 8 | 16 | 2.3 | 50 | -10 | -10 |
| 80 | 94 | 18 | 38 | 0.8 | 55 | -15 | -15 |
| 52 | 92 | 4 | 24 | >5.0 | 40 | +10 | +10 |
| 80 | 84 | 4 | 34 | 0.8 | 40 | -10 | -15 |
| 42 | 88 | 0 | 12 | 2.4 | 50 | -12 | -18 |
| 52 | 88 | 12 | 16 | 1.0 | 50 | -25 | -20 |
| 64±5.2‡ | 89±1.3§ | 7±2.2‡ | 23±3.6‡ | 2.5±0.1‡ | 47±1.1‡ | -10±4.0‡ | -11±3.5‡ |

laboratories (10, 11). It is a phenomenon produced by the bilateral reflex contraction of the intra-aural muscles when either ear is stimulated by high-intensity sound (10), and it bears a reasonably constant relationship to the upper limits of hearing. Direct investigation of the upper limits of hearing entails the risk of producing permanent damage to the hearing mechanism. Thus the CTS which may be evoked by sound intensities which do not cause damage to the ear was chosen to estimate the upper limits of hearing. The sawtooth noise of the audiometer was introduced into the contralateral ear at a level 5 db below the detection threshold previously determined. The 500 cps probe tone was increased in intensity until a threshold response to the tone was obtained. If this postnoise stimulation threshold was the same as determined before noise stimulation, the noise stimulus was increased by 5 or 10 db and the procedure repeated. When the new threshold obtained exceeded the previously determined threshold by at least 5 db for two successive increments of noise, the noise level producing the contralateral threshold shift was recorded in decibels.

RESULTS

Auditory detection and perception in normal subjects. The auditory detection thresholds for frequencies 500 and 1000 cps in 20 normal subjects are presented in Table I. Since the data presented in this paper are related to changes in hearing level for each subject or patient, only changes relative to each subject's detection level need be considered. For the purposes of this study, data for

the normal subjects and for the patients are grouped together irrespective of age.

Values for thresholds and for the loudness judgments (MCLS, ULCLS, DLS, and DLN) are essentially the same as those obtained by other investigators (5, 7, 12). The values for speech discrimination (PB and LPFS, 40 and 60) are also in good agreement with values obtained by other investigators (6, 13). The values obtained for the difference limen and for the CTS are essentially the same as those obtained by other investigators using techniques similar to the ones employed here (8-11).

Auditory detection and perception in patients with adrenal cortical insufficiency receiving no steroid. The auditory detection thresholds for frequencies 500 and 1000 cps in each of the 12 patients with untreated adrenal cortical insufficiency are presented in Table I. Mean detection thresholds for these two frequencies are significantly lower than those for normal subjects, irrespective of age, as shown previously by another technique (3).

The loudness judgments (MCLS, ULCLS, DLS, and DLN) were below those obtained in normal subjects by more than 20 db and were statistically significantly different (Table I). Judgments of DLS, a reliable correlate of the

upper limit of audition, were approximately 30 db below those of normal subjects. The ULCLS in normal subjects is usually 5–10 db below the DLS (7); in these untreated patients the ULCLS was significantly below normal but maintained the relationship of being 5–10 db below the DLS.

Speech discrimination of these patients was significantly impaired. At 40 and 60 db above threshold mean intelligibility scores were more than 20 and 9% below those of normal subjects, respectively. Only two of the subjects attained scores of 100% at 60 db above threshold, whereas this score is common among normal subjects. Although the intensity level at which these words were presented was increased to 70 and 80 db above threshold in the other 10 patients, intelligibility levels did not increase above 94%. Speech discrimination for filtered words was impaired even more. At 40 and 60 db above threshold these patients achieved a mean score of only 6.5 and 23%, respectively. Both scores were significantly below the mean scores of the normal subjects. At 40 db above threshold, 3 of the 12 subjects were unable to recognize even one of the 50 words correctly. This inability to recognize filtered speech did not appear to be primarily intensity dependent, for even though the words were presented at levels up to 90 db above threshold, none of the patients correctly perceived more than 50% of the words.

The ability of patients with untreated adrenal cortical insufficiency to differentiate a steady from a warbling tone was significantly impaired. Four of the patients required about 1.1 db to recognize the tonal change, which is normal for our equipment. Five could not recognize the change even at the 5 db maximum modulation. The average difference limen for untreated patients was 3.3 db or approximately two and one-half times the sound energy required for normal subjects.

The CTS in these subjects is below that for the normal subjects by approximately 30 db, a statistically significant difference (Table I). In normal subjects, the CTS is elicited between 75–90 db. This difference indicates that, "off treatment," the reflex threshold, and hence the upper limit of the auditory range in these patients, is markedly reduced.

The patients had great difficulty in performing other auditory perceptual tasks during the time

they were untreated. Localization of conversational speech more than 30° away from either side of a midline presentation was in error by 15–45°; however, they were able to localize sounds accurately when presented in or very close to the midline. The direction of the error was not consistent. Results of alternate binaural loudness balance tests (ABLB), when performed in the standard manner (14, 15), were within normal limits; i.e., patients could match the loudness of tones presented alternately to the two ears within ± 20 db. However, when presented with a series of "soft" or "loud" comparison tones the patients matched as equally loud tones which differed by as much as 40 db. This phenomenon appeared to be partially dependent upon the duration of the comparison tone, and has been commonly called "anchoring" or stimulus dependence, because the patients tend to make judgments predicated upon prior stimuli more readily than normal subjects. The magnitude of these errors in some patients was such that they were matching as equal tones that were four times as loud or as soft as the standard tone.

The data indicate that, considered as separate groups, patients with either Addison's disease or panhypopituitarism, off treatment, detect and integrate auditory stimuli in a significantly different manner than do normal subjects. The responses of these two groups of patients are statistically the same and can thus be considered as being the same (Tables I and III).

During the time which these auditory perception tasks were performed the patients exhibited both hyponatremia and hyperkalemia (Table I).

Auditory detection and perception in patients with adrenal cortical insufficiency treated with DOCA. The results of the auditory detection and perception tasks performed by the patients with adrenal cortical insufficiency treated with DOCA alone are presented in Table II. The values for the auditory thresholds at 500 and 1000 cps, for the loudness judgments (MCLS, ULCLS, DLS, and DLN), speech discrimination (both filtered and nonfiltered speech), the difference limen, the CTS, the sound localization, and for the ABLB are virtually the same as those observed in patients off treatment (Table I) and are significantly below those obtained in normal subjects despite decreases

TABLE III
Auditory Detection and Perception Thresholds in Adrenal Cortical Insufficiency Treated with Prednisolone

| Patient | Sex | Age | Weight | Serum Na | Serum K | Mean comfort level | Loudness judgments | | | Speech discrimination | | | | Contra-lateral threshold shift | Auditory detection threshold | | | | |
|--|-----|-----------|--------|-----------|---------|--------------------|---------------------------|----------------------------|---------------------------|-----------------------|---------------|--------------|------------------|--------------------------------|------------------------------|---------------------------|---------|----------|----|
| | | | | | | | Upper limit comfort level | Discom-fort level (speech) | Discom-fort level (noise) | PB | LPFS | | Difference limen | | db* | db* | 500 cps | 1000 cps | |
| | | | | | | | | | | | % correct | 40 | | | | | | | 60 |
| | | | | | | | | | | | | | | | | | | | |
| yr | kg | mEq/liter | db* | % correct | 40 | 60 | 40 | 60 | db modulation | db* | db* | 500 cps | 1000 cps | | | | | | |
| Addison's disease | | | | | | | | | | | | | | | | | | | |
| A. B. | F | 54 | 53.30 | 140 | 4.8 | 65 | 77.5 | 82.5 | 56.5 | 90 | 100 | 28 | 44 | 80 | +5 | 0 | | | |
| J. A. E. | F | 33 | 52.64 | 140 | 4.0 | 67.5 | 75 | 80 | 70 | 88 | 100 | 24 | 64 | 70 | 0 | 0 | | | |
| V. McC. | M | 52 | 61.94 | 138 | 5.1 | 70 | 78 | 80 | 95 | 94 | 100 | 36 | 62 | 95 | 0 | 0 | | | |
| Clar. M. | M | 60 | 74.80 | 132 | 4.7 | 70 | 75 | 80 | 83 | 90 | 100 | 26 | 68 | 80 | +20 | +20 | | | |
| P. K. | F | 24 | 47.60 | 142 | 4.8 | 60 | 72.5 | 82.5 | 65 | 100 | 100 | 34 | 66 | 80 | 0 | -10 | | | |
| R. P. | F | 54 | 61.44 | 145 | 4.2 | 70 | 85 | 90 | 76 | 88 | 98 | 32 | 44 | 80 | 0 | -5 | | | |
| R. E. | M | 19 | 50.45 | 138 | 4.3 | 30 | 44 | 78 | 70 | 96 | 96 | 32 | 56 | 82.5 | 0 | 0 | | | |
| Mean \pm SEM | | | | | | | | | | | | | | | | | | | |
| | | | | | | 62 \pm 5.5 | 72 \pm 4.9 | 82 \pm 1.5 | 74 \pm 4.8 | 92 \pm 1.7 | 99 \pm 0.6 | 30 \pm 1.7 | 58 \pm 3.8 | 0.9 \pm 0.2 | 81 \pm 2.7 | 4 \pm 2.6 1 \pm 3.5 | | | |
| Panhypopituitarism | | | | | | | | | | | | | | | | | | | |
| E. B. | M | 57 | 70.68 | 141 | 4.8 | 65 | 72.5 | 80 | 70 | 68 | 72 | 24 | 44 | 70 | -5 | 0 | | | |
| H. R. | M | 18 | 38.39 | 139 | 4.4 | 60 | 65 | 70 | 45 | 88 | 100 | 40 | 60 | 60 | -5 | -5 | | | |
| Mean \pm SEM | | | | | | | | | | | | | | | | | | | |
| | | | | | | 62.5 \pm 2.5 | 69 \pm 3.7 | 75 \pm 5.0 | 57.5 \pm 12.5 | 78 \pm 10 | 86 \pm 14 | 32 \pm 8 | 52 \pm 8 | 1.1 \pm 0.4 | 65 \pm 5 | -5 \pm 0 -2.5 \pm 2.5 | | | |
| Total mean \pm SEM | | | | | | | | | | | | | | | | | | | |
| | | | | | | 62 \pm 4.1 | 72 \pm 3.9 | 80 \pm 1.7 | 70 \pm 4.8 | 89 \pm 3.0 | 96 \pm 3.1 | 31 \pm 2.0 | 56 \pm 3.3 | 0.9 \pm 0.2 | 77.5 \pm 3.3 | +2 \pm 2.5 0 \pm 2.8 | | | |
| Addison's disease (partial) or panhypopituitarism after treatment with ACTH, 40 U/day, 4th day | | | | | | | | | | | | | | | | | | | |
| V. McC. | M | 52 | 62.43 | 133 | 5.3 | 50 | 60 | 80 | 62.5 | 88 | 94 | 30 | 62 | 95 | -5 | -5 | | | |
| Clar. M. | M | 60 | 72.50 | 125 | 5.1 | 70 | 77.5 | 85 | 69 | 78 | 96 | 20 | 28 | 75 | +15 | +15 | | | |
| Clau. M. | M | 18 | 31.90 | | | 70 | 85 | 90 | 90 | 92 | 96 | 34 | 52 | 60 | 0 | 0 | | | |
| Mean \pm SEM | | | | | | | | | | | | | | | | | | | |
| | | | | | | 63 \pm 6.7 | 74 \pm 6.8 | 85 \pm 2.9 | 74 \pm 8.3 | 86 \pm 4.2 | 95 \pm 0.71 | 28 \pm 4.2 | 47 \pm 10.1 | 1.3 \pm 0.2 | 77 \pm 10 | +3 \pm 6.0 +3 \pm 6.0 | | | |

PB, phonetically balanced; LPFS, low-pass filtered speech; ACTH, adrenocorticotropin.
* db hearing level from International Standards Organization (ISO) 1964 Standard.

of serum potassium concentration and gains in body weight.

Auditory detection and perception in patients with adrenal cortical insufficiency treated with prednisolone. The results of the auditory detection and perception tests performed in each patient with adrenal cortical insufficiency treated only with prednisolone, 20 mg/day, for 2–4 days, are presented in Table III. In all patients, either with Addison's disease or with panhypopituitarism, the auditory detection thresholds for 500 and 1000 cps increased significantly as has been previously shown (3). Loudness judgments changed significantly and fell within the normal range for each measurement made; the MCLS increased approximately 20 db over the untreated state, as did the ULCLS, the DLS, and the DLN. Speech discrimination improved significantly for both filtered and nonfiltered words and returned to scores similar to those obtained for normal subjects by ourselves and by other investigators (13). The difference limen for intensity decreased significantly by more than 2 db and returned to the values obtained in normal subjects as did the values for the contralateral threshold shift.

This increase in ability to perform auditory perceptual tasks associated with a decrease in auditory detection sensitivity occurred after treatment with maintenance doses of carbohydrate-active steroid alone or together with maintenance doses of sodium-potassium-active steroid added; this occurred both in patients with Addison's disease and with panhypopituitarism. Similarly, in those patients with adrenal cortical insufficiency with some remaining cortical function or with panhypopituitarism, treatment with ACTH for 4 days significantly increased the patient's ability to perform these varied auditory perceptual tasks as effectively as treatment with carbohydrate-active steroids (Table III).

DISCUSSION

The meaning of the loudness judgments and of the CTS may be evaluated more clearly by comparing the response levels of normal subjects with those of patients with untreated adrenal cortical insufficiency (Fig. 1). The auditory detection thresholds of the patients are significantly below those of the normal subjects, as previously described (3). This illustrates, once again, their extreme sensitivity at the lower end of the dynamic range of hearing.

However, the normal ear can accommodate to changes in sound power over a range of approximately 10^{14} power units between detection of an auditory signal to painful stimulation or maximum-tolerated sound (6). Judgments of discomforting loudness (DLS, DLN) and the CTS are related to the upper limits of auditory capacity, being elicited at about 80 db (10^8 power units) above detection threshold (16). Our data show that the DLS and the CTS are evoked at a mean level of 83 db above normal hearing threshold (Table I). By contrast, patients with untreated adrenal cortical insufficiency demonstrate mean CTS levels that are shifted downward even more markedly than their tonal detection thresholds; e.g., the CTS at 500 cps is evoked at 63 db above the mean 500 cps detection threshold of -12 db (Fig. 1). This corresponds to a reduction of the dynamic range of auditory capacity by a factor of 10^2 power units; thus, the maximum tolerable loudness for patients with untreated adrenal cortical insufficiency is approximately 1/100th of that for normal subjects. Moreover, judgments of the mid-range of loudness (MCLS, ULCLS) indicate that in patients with untreated adrenal cortical insufficiency compression takes place nonlinearly, occurring most markedly in the upper portion of auditory range. This is an unusual finding for, in most cochlear disorders, there is compression only at the lower end of the dynamic range (a sensitivity loss), whereas the upper limits remain virtually intact (16). These findings correlate well with subjective reports of the patients, who state that "off treatment," stimuli which normally do not annoy them produce discomfort to such degree that these are the major complaints of many of them. We would also infer from these data that patients with untreated adrenal cortical insufficiency are more sensitive to painful auditory stimuli as they are to painful stimuli of other modalities (17). When the patients are treated with carbohydrate-active steroid all loudness judgments (MCLS, ULCLS, DLS, DLN) and the CTS return to levels observed in normal subjects.

Results of the difference limen indicate that patients with untreated adrenal cortical insufficiency experience difficulty in perceiving small increments in sound intensity when untreated or treated with DOCA. When treated with carbohydrate-active steroid their responses were not significantly different from normal. Although this measurement

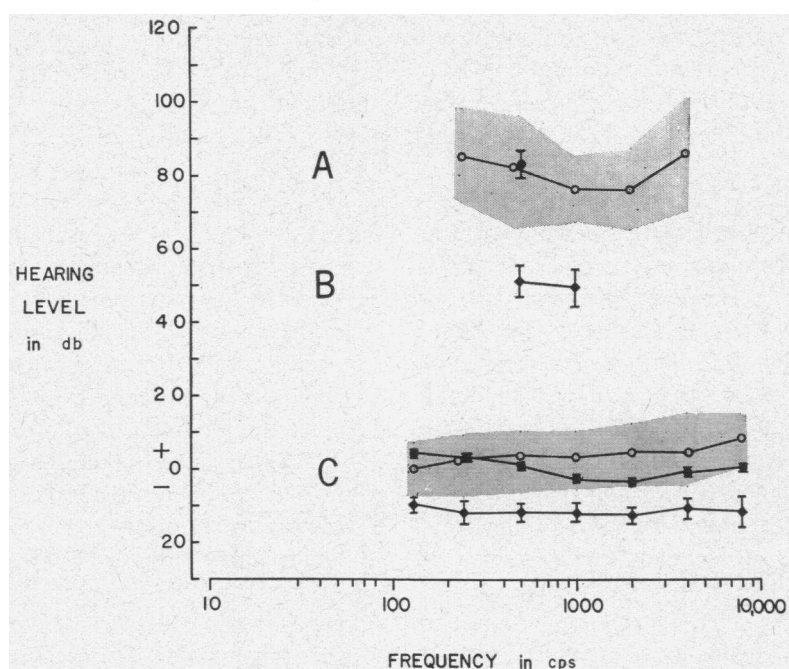


FIGURE 1 Comparison of audiometric thresholds and contralateral threshold shifts (CTS) in normal subjects with those in patients with adrenal cortical insufficiency, off treatment. *A*, The open circles at the top of the figure represent the mean CTS determined in 44 normal subjects, aged 15-34, by Jepson (16); the upper and lower limits of the upper gray area represent the range of these responses (16). The closed circle within the upper gray area represents the mean CTS determined in the 20 normal subjects of this study. The lines above and below this closed circle represents ± 1 SEM. Data for the CTS at 500 cps in the subjects of this study are similar to that obtained by Jepson. *B*, The closed diamonds directly below the upper gray area represent the mean CTS obtained in this study of 12 patients with adrenal cortical insufficiency, off treatment, aged 19-57; the lines above and below these rectangles represents ± 1 SEM. *C*, The open circles at the bottom of the figure represent the mean audiometric thresholds in normal subjects obtained by Jepson (16), the lower gray area, the range of these thresholds. The closed circles within the lower gray area represent the audiometric thresholds obtained in the normal subjects of this study. The lines above and below the circles represent ± 1 SEM. The closed diamonds below the lower gray area represent the audiometric thresholds obtained in patients with adrenal cortical insufficiency, off treatment. The lines above and below the rectangles represent ± 1 SEM. At each frequency both mean audiometric threshold and CTS for the patients with adrenal cortical insufficiency were significantly below those of either group of normal subjects.

has been criticized as unreliable because of the difficulty of the judgments involved (8, 18) the magnitude of the changes indicates that the differences are indeed meaningful. This test indicates cochlear disease when the difference limen is small (8, 9). The present results indicate that either "off treatment" or "on DOCA" the patients demonstrate normal cochlear function.

The speech discrimination tests were designed to examine another parameter of perceptual or

"integrative" capacity. Patients with untreated adrenal cortical insufficiency exhibited grossly impaired ability to "integrate" speech stimuli into meaningful patterns. Similar results were shown by the failure of the untreated or DOCA-treated patients to perform sound localization tasks or ABLB, whereas after treatment with carbohydrate-active steroid they performed these tasks normally. The anatomical localization of this perceptual defect is not clear. Patients with cortical

auditory impairment, e.g. after temporal lobectomy or with temporal lobe tumors, generally display normal or slightly depressed discrimination scores for unfiltered words. Since there is bilateral representation in the cortex, and since tumors are rarely bilateral, this result might be expected. Patients with eighth nerve defects or mild cochlear impairments exhibit impaired speech discrimination scores (19, 20). However, discrimination for filtered speech is relatively unaffected by lesions below the brain stem but markedly impaired with cortical involvement (20). The striking inability of these patients to perform the ABLB, a task which normal subjects perform with precision (14), has been observed previously, with a similar degree of impairment, in patients with lesions in auditory pathways between cochlea and brain stem (19, 20). Thus, untreated or DOCA-treated patients present a pattern of altered perception consistent with a cortical abnormality, but their multiple auditory abnormalities suggest a very complex phenomenon unrelated to any specific anatomical lesion. Rather, the results are more suggestive of a diffuse metabolic abnormality. This inference seems supported by the fact that increased detection sensitivity occurs in virtually all sensory modalities in patients with untreated adrenal cortical insufficiency (1-3, 21).¹

One explanation for the "integrative defect" which occurs after removal of carbohydrate-active steroid is that timing of transmission of neural impulses in both the central and peripheral nervous systems is significantly altered. Subjective responses of these patients support this hypothesis. For example, sound localization, when the sound source is in the midline, is essentially normal, whereas localization is markedly in error when the source is more than about 30° from the midline. These results suggest that it is the temporal factor in sound localization that is critical for these patients. If the signal arrived at the two ears at the same time, i.e. if the sound source was in the midline, the patients were able to make an appropriate judgment of sound azimuth. However, when the time of arrival of the signal at the two ears became disparate beyond a few milliseconds, i.e. when the azimuth increased to 30° or greater, they were unable to make a correct judgment.

¹ Daly, R. L., and R. I. Henkin. Auditory function in adrenal insufficiency. Data in preparation.

Similarly, the increase in harshness or the "rasping" quality of the experimenter's voice which the untreated or DOCA-treated patients reported while in the sound chamber (3) is interesting in this respect, for these patients did not perceive this quality when they were treated with carbohydrate-active steroid. This effect can be produced in speech by altering frequency and intensity relationships, or by altering temporal relations, e.g., by rapid switching or "flickering" of the signal. No defect existed in our electronic equipment which could adequately account for this phenomenon in terms of frequency or intensity distortion. We therefore suggest that the effect may be the result of a distortion in the patient's appreciation of temporal relationships.

Abnormalities in both peripheral nerve conduction velocity and visual cortical-evoked potentials among patients with adrenal cortical insufficiency support this hypothesis. Previous studies from this laboratory have demonstrated that ulnar nerve conduction velocity in untreated or DOCA-treated patients with adrenal cortical insufficiency was increased above normal, due to a small decrease of 0.5-1 msec in the time over which the nerve impulse traversed the nerve from elbow to wrist (21). After treatment with carbohydrate-active steroid this axonal conduction velocity returned to normal, the conduction time increasing to normal (22). These same studies have also indicated that the time of conduction of the nerve impulse across the myoneural junction studied was significantly increased above normal by 1.5-3 msec.² Studies of visual and auditory cortical-evoked potentials in these untreated or DOCA-treated patients have demonstrated a significant increase in latency of their responses when compared to their latencies after treatment with carbohydrate-active steroids. These increases in latency were of the order of 5-30 msec and were presumably due to the summation of synaptic delay as the impulse traversed the multisynaptic visual and (or) auditory systems (23). The most marked increases in latency, more than 15 msec, occurred in the later, nonspecific portions of the evoked response, i.e., portions associated with reticular formation activity (23). Less marked but still significant increases in latency of 5-10 msec also occurred in the specific, earlier portions of the evoked response (23).

² Henkin, R. I. Unpublished observations.

When these patients were treated with carbohydrate-active steroid all latency changes reverted to normal (23). These results correlate well with similar results obtained in adrenalectomized animals both by ourselves as well as by other investigators. These results suggest that increases in latency of cortical-evoked potentials occur in response to stimuli such as electrical stimulation, touch, or pain (23-26); latencies also return to normal after treatment with carbohydrate-active steroids (23, 26). These increases in latency "off treatment" were considered to be due to increases in synaptic delay. Indeed, preliminary results from this laboratory suggest that adrenalectomy and subsequent treatment with carbohydrate-active steroid produces changes in synaptic delay as measured by microelectrode implantation across one synapse in the spinal cord of the cat.³

Perception and integration of sensory stimuli in the visual and auditory systems have been related, by numerous investigators, to the timed arrival of sensory stimuli in the cortex (27, 28). The small increases in conduction velocity along peripheral axons coupled with the large increases in latency in multisynaptic sensory systems observed in these patients may well result in a markedly abnormal pattern of neural stimuli reaching the cortex. This pattern (coding) presumably could not be interpreted in a normal fashion, and the result might be an impairment of perception, such as that which we observed. In addition, the sum total of conduction from the time of depolarization at the sensory end organ to final cortical perception is significantly delayed in these patients due to the large increase in synaptic delay. This also might contribute to their perceptual impairment. Whatever the hypothesized mechanism, the institution of treatment with carbohydrate-active steroid returns neural conduction and sensory integration to normal. Since we have observed no specific change in either detection, perception, or neural transmission after treatment with DOCA, we suggest that changes in extracellular sodium, potassium, or fluid volume have little effect upon this phenomenon.

The increased detection sensitivity observed in these patients may not be primarily related to alterations in neural transmission. Alternatively, these changes may be due to an increase in excita-

bility of the nervous system after removal of carbohydrate-active steroid; i.e., depolarization of the nerve membrane may occur at a lower threshold than it would were carbohydrate-active steroid normally present.

Other investigators have suggested this possibility after studying the in vitro electrical characteristics of sciatic nerves taken from adrenalectomized rats (29). We have obtained only fragmentary data in patients to support this hypothesis. In some patients maximum contraction of the abductor digiti quinti, the muscle used in the measurement of ulnar nerve conduction velocity, could be obtained with the imposition of a significantly lower voltage than that needed in the patients when they were treated with carbohydrate-active steroid.² Similarly, amplitude of response to light in the visual evoked cortical potentials is markedly increased in some untreated or DOCA-treated patients as compared to the responses of these same patients treated with carbohydrate-active steroid.²

The explanation of these phenomena is not known. However, the consistency with which the increase in detection sensitivity accompanies the decrease in perception or integration in these patients is impressive. A reinterpretation of data obtained from studies dealing with sensory deprivation or various forms of "schizophrenia" suggest that a similar dissociation between detection and perception may be inferred (30-32). Studies of auditory detection and integrative functions in patients under the influence of various drugs, including lysergic acid diethylamide, also suggest a similar dissociation (21). We can hypothesize that a specific relationship exists at all times between detection and perception. If detection were normally set at a "low gain" to allow maximal integration of all incoming sensory stimuli, and if carbohydrate-active steroid were to play a role in the control of the input of sensory stimuli through a negative feedback mechanism, then removal of carbohydrate-active steroid from the system would significantly alter the normal gain-control mechanism; the nervous system would be bombarded with sensory stimuli which normally would be rejected. Further, this would occur in the nervous system at the expense of stimulus integration.

The mechanisms underlying these phenomena are complex, and these studies represent only a

³ Evans, E., and R. I. Henkin. Unpublished observations.

beginning in their elucidation. However, the relationship between detection and integration and the role which steroid hormones play in conduction of the neural impulse both along the axon and across the synapse are important for understanding the manner in which the endocrine and the nervous systems interact.

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