

## Reduction of Adrenocorticotrophic Hormone (ACTH) and Cortisol in Drug Addicts Treated by Acupuncture and Electrical Stimulation (AES)\*

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Forty-two heroin addicts and 31 normal persons were examined for the effect of acupuncture and electrical stimulation (AES) on plasma ACTH, cortisol and cyclic-AMP levels. Both ACTH and cortisol levels were reduced significantly in the addicts after treatment whereas no such significant reduction was observed in the normals. Plasma cyclic-AMP level was not affected in either group. Taken together, results from the present study suggest that the mechanism of AES in the treatment of addiction may have a neuroendocrinological basis. This hypothesis is particularly attractive in view of the isolation of opiate-like peptides from the brain.

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### INTRODUCTION

Acupuncture with electrical stimulation (AES) has been successfully used since 1972 for the treatment of abstinence symptoms associated with opiate addiction [1-4]. Subjects addicted to hard drugs, such as opium or heroin, usually show a marked reduction of withdrawal symptoms when treated with AES for only 15 to 30 minutes. Moreover, the effect of AES can sometimes last up to several hours depending on the degree of addiction. Because of this long lasting effect we suspect that AES may exert its action by stimulating certain neuroendocrine systems. Against this background, we have made a preliminary examination of the possibility of biochemical changes associated with this type of treatment [5]. Our results indicate that AES has a suppressive effect on the plasma ACTH, cortisol and cyclic-AMP levels.

In this paper, we wish to report the results of an expanded study on the effect of AES on the levels of these compounds in both addicted and normal subjects. It was hoped that with a larger sample size, a more precise and accurate evaluation of these parameters could be made.

### MATERIALS AND METHODS

#### *Subjects' background*

Thirty-two male and 8 female addicts were examined in this study, all except one male and one female being Chinese. Both the male and female subjects were

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voluntarily hospitalized during the treatment period. For the male subjects, the average length of addiction was 9.3 years with a range of from 2 to 27 years. Sixteen of the patients took heroin by inhalation and the rest by intravenous injection. The average body weight of the male subjects was 116 lbs. The length of addiction for the female group was from 10 months to 15 years with an average of 5 years. All the females took heroin by inhalation except one who used injections. Their average body weight was 104 lbs.

The normal control group for this study consisted of 31 subjects, 17 male and 14 female, all healthy Chinese. Their ages ranged from 20 to 50 years with an average of 24.2 years. The average body weight was 123 lbs.

### *Method and program of treatment*

Upon admission to the treatment clinic, 15 of the 32 male addicts and all the female addicts were given methadone for three days, starting with 30 mg on the first day and then 20 and 10 mg, respectively, on the second and third days. This group of addicts was designated as the methadone pre-treated group. None of them had any more methadone after the beginning of AES treatment. The other 17 male addicts received no other form of treatment apart from AES. All the addicts were treated for seven days, as previously described [5].

The technique of AES treatment consisted of cleaning the concha of both ears with an alcohol cotton wool swab. Then a sterile, half-inch stainless-steel acupuncture needle, gauge 30, was inserted subcutaneously on each side of the ear about 3 to 5 mm deep. The needles were then connected to an electrical stimulator, running on a 12V battery. The pulse frequency used was 125 Hz. On the average, only 5 to 6V were required by the subjects. However, some patients required more voltage, depending on the duration of their addiction, the quality of the drug taken and the method used.

When the intensity of the electrical stimulation was increased, the subject felt vibrations passing through the needles in each concha, much like the buzzing of a mosquito. Too much current would produce pain, headache, nausea, vomiting and sometimes even skin-burn. It is advisable to ascertain whether the patient feels the current "tickling" in the ear. If so, treatment should be stopped at this point. Usually, after 5 or 10 minutes, the subject will no longer feel the current and then the intensity should again be gradually increased. The duration of treatment was 30 minutes.

### *Sampling*

Based on the results of our preliminary study [5], the most pronounced change in hormonal levels occurred during the initial AES treatment. In view of this, we have limited our present study to the evaluation of biochemical changes occurring during the first treatment session.

Blood samples were obtained from the subjects between 9:00 to 10:00 A.M. by venepuncture. They were collected in tubes containing either heparin or EDTA as anti-coagulants. The blood obtained in this way was immediately cooled in an ice-bath. Plasma was separated from the blood cells by low-speed centrifugation (3,000 xg) and frozen at  $-20^{\circ}\text{C}$  to keep until needed. Since from some of the subjects we were not able to obtain enough blood for all the analyses, the total number of patients examined was less than 40 (see column 2, Tables 1, 2 and 3).

### *Assay procedure*

The ACTH, cortisol and cyclic-AMP levels in the plasma were determined by using commercially available radioimmunoassay kits from the New England Nuclear

TABLE 1  
Plasma ACTH (pg/ml) levels of heroin-addicted and normal subjects before and after AES treatment

Subjects	Cases examined	Pre-AES	Post-AES	% Change	Test of significance by difference*
All addicts	26	25.9 ± 18.4	21.3 ± 17.4	-17	0.010 > p > 0.001
Male addicts	19	26.0 ± 20.7	23.0 ± 19.8	-12	0.100 > p > 0.050
Female addicts	7	25.4 ± 11.2	16.7 ± 7.3	-34	0.025 > p > 0.010
All normal	19	18.2 ± 9.0	18.2 ± 7.8	-3	n.s.
Male normal	12	17.0 ± 10.1	21.2 ± 6.7	+24	0.100 > p > 0.050
Female normal	7	21.4 ± 6.5	13.2 ± 7.5	-38	0.100 > p > 0.050

\*In this and subsequent tables, the *t*-test was performed on the difference between the pre- and the post-values in individual cases and not on the difference between the mean pre- and post-values.

n.s., not significant,  $p > 0.1$ .

TABLE 2  
Plasma cortisol ( $\mu$ g/100 ml) levels of heroin-addicted and normal subjects before and after AES treatment

Subjects	Cases examined	Pre-AES	Post-AES	% Change	Test of significance by difference
All addicts	34	20.3 ± 13.0	17.2 ± 11.2	-15	0.050 > p > 0.020
Male addicts	26	19.2 ± 12.7	17.6 ± 12.3	-8	n.s.
Female addicts	8	23.8 ± 14.2	15.7 ± 7.4	-34	0.050 > p > 0.020
All normal	30	13.8 ± 8.2	13.0 ± 9.3	-6	n.s.
Male normal	17	10.2 ± 5.5	10.2 ± 4.6	-3	n.s.
Female normal	13	18.1 ± 9.2	16.7 ± 12.4	-8	n.s.

TABLE 3  
Plasma cyclic-AMP (pmol/ml) levels of heroin-addicted and normal subjects before and after AES treatment

Subjects	Cases examined	Pre-AES	Post-AES	% Change	Test of significance by difference
All addicts	32	8.0 ± 4.8	7.5 ± 5.5	-6	n.s.
Male addicts	25	8.0 ± 4.9	8.3 ± 5.7	+4	n.s.
Female addicts	7	7.9 ± 4.6	4.6 ± 3.4	-42	n.s.
All normal	31	9.9 ± 3.9	9.5 ± 3.2	-5	n.s.
Male normal	17	10.0 ± 3.1	9.5 ± 3.2	-4	n.s.
Female normal	14	9.8 ± 4.9	9.4 ± 3.3	-5	n.s.

Corporation, Worcester, Mass., U.S.A. (for cortisol) or from the Radiochemical Centre, Bucks., U.K. (for ACTH and cyclic-AMP). The procedures used in this study were essentially those recommended by the manufacturers. Radioactive counting was carried out, using either a Nuclear Chicago, Mark I (Des Plaines, Ill., U.S.A.) liquid scintillation counter or a gamma counter of a similar make. All the samples were counted to a statistical margin of error of less than one percent, at a 95% confidence level.

### Statistical tests

In the present study, statistical analyses on individual data of the subjects were pooled and presented as the mean plus and minus one standard deviation. The

Student's t-test was used to evaluate the significance of the difference in the plasma concentrations of the compounds tested before and after AES. Except in borderline situation, a  $p < 0.05$  was considered to be significantly different.

## RESULTS

As methadone pre-treatment did not seem to have any effect on biochemical changes during AES treatment, we decided to pool the data of the methadone pre-treated and the un-pretreated groups for evaluation.

Examination of the mean plasma ACTH and cortisol levels of the addicted group reveals a significant net reduction of 17% ( $0.01 > p > 0.001$ ) and 15% ( $0.05 > p > 0.02$ ) in the levels of these hormones after AES treatment (Tables 1 and 2). When the addicted group was separated by sex, the plasma ACTH and cortisol level of the female addicts showed a significant reduction while no such marked reduction was observed in their male counterparts. In the normal subjects, both ACTH and cortisol levels showed no significant net changes before and after AES. However, if data for the male and the female subjects were analyzed separately, the plasma ACTH level tended to increase with the male and decrease with the female after AES treatment. Whether a person's sex makes a difference as far as AES treatment is concerned is an open question. In contrast to ACTH and cortisol, the average plasma cyclic-AMP level in both the addicted and the normal subjects was not altered by AES treatment (Table 3).

Comparison of the pre-AES ACTH, cortisol and cyclic-AMP levels between the addicted and the normal group indicates that the average ACTH and cortisol levels of the former group were higher by about 42% ( $0.1 > p > 0.05$ ) and 32% ( $0.05 > p > 0.02$ ), respectively. On the other hand, the average plasma cyclic-AMP level of the addicted subjects was lower by about 19% ( $0.1 > p > 0.05$ ). The higher ACTH and cortisol levels in the addicted group were probably due to the effect of drug withdrawal since these patients were given no narcotics for 12 hours prior to AES treatment.

## DISCUSSION

The biochemical basis of drug addiction and the mechanism of acupuncture with electrical stimulation (AES) in ameliorating withdrawal symptoms are, by and large, unknown. We have, in this study, examined the plasma ACTH, cortisol and cyclic-AMP levels in both heroin-addicted and normal subjects, before and after AES treatment. According to our data, initial AES treatment appears to be effective in reducing the plasma ACTH and cortisol levels of heroin addicts but not of their normal counterparts. This differential action may be due to the effect of heroin addiction in changing the response of the neuroendocrine system to AES. Renault et al. [6] have demonstrated that elevation of plasma cortisol levels in methadone-maintained addicts usually precedes the appearance of abstinence symptoms. In this connection, the suppression of ACTH and cortisol levels may be taken as an indication of how this technique can act on the pituitary-adrenal axis to avert and ameliorate abstinence symptoms.

The recent isolation of a number of peptides, having opiate-like activity, from the pituitary and the hypothalamic regions has prompted speculation that the analgesic action produced by acupuncture may be related to the secretion of these compounds [7,8]. As both the opiate-like peptides and ACTH are believed to be derived from the same parent molecule [9], it is not unreasonable to assume that there is an association

between the physiological levels of these compounds. Our demonstration that AES can affect the plasma level of ACTH in drug addicts suggests that the levels of the opiate-like peptides may also be affected. In this respect, Guillemin et al. [10] have recently obtained evidence to indicate that  $\beta$ -endorphin and ACTH are secreted concomitantly into the bloodstream. If this is the situation, our present result would imply a lower level of  $\beta$ -endorphin in the blood after AES. Clearly, this contradicts the idea of using  $\beta$ -endorphin to explain the action of AES. In order to resolve this dilemma, we are currently measuring the  $\beta$ -endorphin level in both the brain and blood of experimental animals during the treatment of addiction by AES.

In contrast to ACTH and cortisol, the plasma cyclic-AMP level did not show any significant changes in either the addicted or the normal subjects, after AES treatment. Despite this, in the female addicted group, there was a large but statistically insignificant reduction in the net plasma cyclic-AMP level. In view of the small number of female addicts whom we have examined here, the significance of this reduction can only be evaluated after additional data become available.

Based on results of *in vitro* experiments, Sharma et al. [11] hypothesized that the cellular cyclic-AMP level is probably suppressed during addiction and becomes elevated upon withdrawal. Since one of the actions of AES is to suppress the onset of withdrawal, the cellular cyclic-AMP level should, according to Sharma's theory, show a decrease after acupuncture. Of course, our inability to observe a decrease of cyclic-AMP level in the plasma after AES cannot be regarded as equivalent to no change having occurred at the cellular or tissue level.

It has been reported that animal experiments conducted in China show that acupuncture can reduce the level of ascorbic acid in the adrenal gland [12]. This reduction was found to be more pronounced in female than in male rats. Our present findings also indicate, with regard to ACTH secretion, that there may be a sex difference in the response to AES treatment. At present, we cannot offer a valid explanation to account for this.

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