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SUPPRESSION OF NARCOTIC WITHDRAWALS AND PLASMA ACTH BY AURICULAR ELECTROACUPUNCTURE*

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SUMMARY: Auricular electroacupuncture (AES) has been found to be successful in the suppression of withdrawal symptoms of morphine-addicted mice. In abrupt withdrawals precipited by naloxone, the plasma adrenocorticotropin (ACTH) rises to a high level which can also be effectively suppressed by AES. This elevation of plasma ACTH is not due to naloxone, as naloxone has no effect on the ACTH level in non-addicted mice. The possible physiological effect produced by AES is discussed.

Analgesia produced by acupuncture is well established (1). A number of reports have demonstrated the effective use of acupuncture in surgical operation as well as various types of diseases (2-5). In animal studies, Pomeranz and Chiu (6) showed that electroacupuncture in awake mice produced analgesia to noxious heat stimuli. Since 1972, Wen and Cheung (7) have applied AES successfully in the treatment of morphine addiction in over 600 cases. Clinical evidence has firmly established that AES is effective in relieving withdrawal pains (8-11). Our present findings support the above clinical phenomenon when experimented on morphine-addicted animals. The withdrawal symptoms of morphine-addicted

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Abbreviations: AES, auricular electroacupuncture; ACTH, adrenocorticotropic hormone; RIA, radioimmune assay.

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animals induced by naloxone (12) was found to be suppressed by AES. During withdrawals, the plasma ACTH of the addicted mice was found to rise to a very high level as a result of stress produced by morphine abstinence. Whereas this high level of ACTH can be reduced by the application of AES. This result is complementary to the results obtained from human drugs addicts (13, 14).

MATERIALS AND METHODS

Morphine hydrochloride was obtained from British Drug House, England, naloxone was supplied by Endo Lab. Inc., N.Y. RIA kit for ACTH was purchased from Radiochemical Centre, Amersham, England.

Acupuncture with electrical stimulation (AES) was performed in such manner that both ears of the mouse were inserted with a small needle (0.5 cm long, gauge 34) at the middle of the conchae corresponding to the lung point of the human (7). These needles were connected to an electric wire from a transitorized pulse generator which provides a biphasic square wave with a frequency of 120 Hz (Biopulse Ltd., Hong Kong). The voltage was adjusted to 0.5 to 1 volt.

Female mice of WHT strain (British) weighing 25 to 30 gm were bred in our animal house and kept in light (6:00-18:00 h), temperature and humidity controlled rooms. Mice were housed 8-9 per cage and given food and water *ad libitum*. The animals were rendered dependent on morphine by the subcutaneous implantation of 2 morphine pellets with an interval of 24 h. All animals were experimented 24 h after the second implantation. The morphine pellets were prepared and implanted according to the method of Hui and Roberts (15). Experimental mice were housed in the laboratory for overnight stabilization with only water provided. Addicted mice were separated into two groups and withdrawal was induced by intraperitoneal injection of 0.1 ml naloxone in a dosage of 10 mg/Kg of body weight (16). One group of the addicted animals was primed with AES for 30 min prior to naloxone injection and followed by AES treatment for another 15 min. The other group received no AES treatment. In both cases, withdrawal symptoms were monitored for 15 min after the naloxone injection. The degree of withdrawal was assessed by counting the total scores of jumping, abnormal posturing, diarrhea and body shaking in 15 min as described by Maggiolo and Huidobro (17).

For ACTH assay, the animals were decapitated and blood samples were collected in heparinized tubes. Plasma ACTH was determined using the commercial RIA kit. The procedures were as described by the manufacturer.

RESULTS AND DISCUSSIONS

Naloxone at several concentrations, 5, 10 and 20 mg/Kg induced withdrawal symptoms in morphine-addicted mice, and optimal withdrawal scores were obtained with 10 mg/Kg of naloxone (Fig. 1). This concentration was therefore used in all following studies. Auricular electroacupuncture significantly decreased total withdrawal scores induced by naloxone (Fig. 1). This decrease is most obvious when withdrawal symptoms were induced

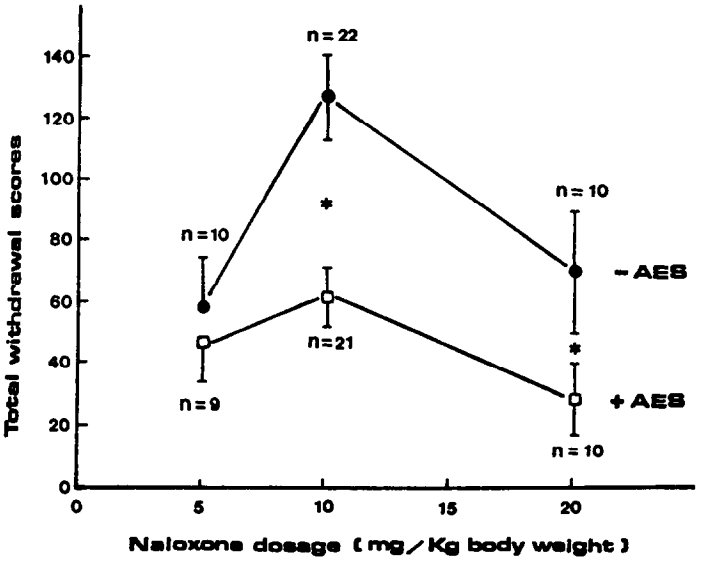

Fig. 1. Total scores of naloxone-precipitated withdrawal. n: no. of mice; *: statistically significant; ●—●—● : withdrawal scores without AES; □—□—□ : withdrawal scores with AES.

by 10 mg/Kg of naloxone ($p<0.001$). Significant decrease of withdrawal scores was also observed when withdrawal symptoms were precipitated by 20 mg/Kg of naloxone ($p<0.05$); while 5 mg/Kg of naloxone was not significant.

In agreement with our previous clinical studies, we have found that the plasma level of ACTH in morphine-addicted mice (46.8 pg/ml) is only one-third that of the non-addicted mice (114.7 pg/ml). Mice injected with naloxone or saline do not show any significant changes in plasma level of ACTH. However, naloxone caused a ten-fold increase in plasma ACTH in morphine-addicted mice (46.8 to 446.4 pg/ml). This increase is significantly reduced by AES to approximately the normal level (186.6 pg/ml) (Table 1). Similar plasma ACTH elevation in human addicts due to naloxone precipitated withdrawal has been reported (18). This has been interpreted as due to excess stress generated by morphine withdrawal. ACTH has been recognized as the primary pituitary hormone

Table 1

Effect of AES on Plasma ACTH of Addicted Mice during Withdrawal

Group	ACTH (pg/ml) ± S.D.
Addicted + naloxone	446.4 ± 236.5 (9)
Addicted + naloxone + AES	186.6 ± 143.2 (8)

secreted in response to acute stress in all species (19). Preliminary studies in our laboratory have also demonstrated that AES has no effect on plasma ACTH level in non-addicted rats (manuscript in preparation). Our findings thus suggest that AES is effective in lowering plasma ACTH level in naloxone precipitated morphine-addicted mice. It is well-established that opiate-like peptides are associated with the development of acute tolerance and cross tolerance to morphine (20, 21, 22) and naloxone-induced abstinence in rodents (23, 24). Thus the concommitant reduction of plasma ACTH level to its normal value and the suppression of withdrawal symptoms in naloxone precipitated mice by AES suggests an interrelationship between endogenous opiate-like peptides and plasma ACTH level.

It is of interest to note that both ACTH and β-endorphin are released at the same time in non-addicted animal (25). Since both ACTH and endogenous opiate-like peptides (β-endorphin and enkephalins) have been postulated to be derived from one pro-hormone molecule secreted by anterior pituitary, it appears that the action of AES is to suppress the production and/or release of such pro-hormone from brain, thus rendering lower levels of ACTH in blood. In human addicts, the blood ACTH is reduced after AES treatment (26).

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