

# Failure of $\alpha$ -MSH to Delay Extinction of Conditioned Avoidance Behavior in Rats with Lesions in the Parafascicular Nuclei of the Thalamus

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BOHUS, B. AND D. DE WIED. *Failure of  $\alpha$ -MSH to delay extinction of conditioned avoidance behavior in rats with lesions in the parafascicular nuclei of the thalamus.* *PHYSIOL. BEHAV.* 2(2) 221-223, 1967. Bilateral lesions in the thalamic parafascicular area facilitate the rate of extinction of a conditioned avoidance response without affecting avoidance learning. Treatment with long-acting  $\alpha$ -MSH during extinction failed to affect the rate of extinction of the avoidance response. Since this peptide delays extinction of the avoidance response in posterior lobectomized rats in which a similar rapid rate of extinction is found as in rats with lesions in the parafascicular nuclei (De Wied, 1965), the results stress the importance of the central nervous system for the effect of  $\alpha$ -MSH on conditioned avoidance behavior.

$\alpha$ -MSH      Extinction of conditioned avoidance response      Parafascicular nuclei      Lesions

EFFECTS of ACTH or corticosteroids on either active [1, 2, 3, 7, 12, 16, 17] or passive [14, 15] avoidance behavior have been described during the past decade. Removal of the posterior pituitary facilitates extinction of an avoidance response while the administration of ACTH,  $\alpha$ -MSH or  $\beta$ -MSH during the extinction period maintains avoidance behavior of the posterior lobectomized rat [8]. Rats with lesions in the parafascicular nuclei of the thalamus like posterior lobectomized rats rapidly extinguish a conditioned avoidance response. Since  $\alpha$ -MSH had been shown to delay the rate of extinction of the avoidance response in posterior lobectomized rats [8], the effect of  $\alpha$ -MSH treatment was studied on extinction of a similar conditioned avoidance response in rats bearing bilateral lesions in the parafascicular region of the thalamus in an attempt to localize the "site" of action of ACTH-like peptides on conditioned avoidance behavior.

## METHODS

A total of fifty male albino rats of an inbred strain were used. The rats weighed 120-130 g at the time of operation.

Destruction of the parafascicular region of the thalamus was performed under ether anesthesia by high frequency electrocauterization with the following parameters: 40 mA d.c. for 4 msec [5]. Bilateral lesions were made using a stainless steel electrode which was inserted stereotaxically

into the appropriate thalamic areas. Control rats were sham-operated by inserting the electrode without applying the current.

The rats were allowed to recover for two weeks before conditioning was begun. Avoidance conditioning was performed in a shuttle-box described by Murphy and Miller [17]. The box was divided into two equal compartments by a 2 in. barrier. Each compartment had a grid floor through which the unconditioned stimulus (US) of shock (25 V; 1.8 mA) was delivered to the feet of rats. The sound of a buzzer served as the conditioned stimulus (CS). The CS was presented 5 sec prior to the US. If the animal crossed the barrier within 5 sec, the CS was immediately terminated and the rat avoided shock.

Rats were placed into the shuttle-box 1 min prior to the first trial. Ten conditioning trials were given every day for 14 days.

The mean intertrial interval was progressively reduced after every three sessions from a mean of 60 sec, in the beginning to 20 sec for the last two sessions of the 14-day period of learning. This procedure results in resistance to extinction [18]. As a criterion of learning 80 per cent or more conditioned avoidance responses (CAR's) during the last three consecutive sessions was chosen. Rats which achieved the criterion of learning were subjected to extinction sessions for the next 14 days. Extinction training was carried out following the same schedule as had been used during the last two sessions of conditioning except that the US of shock

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was never presented and the CS was terminated after 5 sec if an avoidance response had not occurred.

Those rats with bilateral lesions in the thalamic parafascicular nuclei which had reached the criterion of learning were divided into two groups at random before extinction sessions were started. These groups were treated either with synthetic  $\alpha$ -MSH (Ciba, Basle) or with a placebo.  $\alpha$ -MSH was given as a long-acting Zn-phosphate preparation in a dose of 10  $\mu$ g per rat [9]. The placebo consisted of Zn-phosphate without the addition of peptide. Both substances were given subcutaneously every other day 2 hr prior to the daily sessions. The first injection was given on the last day of avoidance learning after the session.

Following the last extinction trial rats were sacrificed and their brains were fixed in formaline. Histological verification of the localization of the lesions was performed in unstained frozen sections by the method of Guzman-Flores *et al.* [11].

in the two groups of rats with a parafascicular lesion and to  $113.5 \pm 6.0$  in sham-operated controls.

Significant differences in avoidance behavior between rats with lesions and sham-operated animals were found during extinction (Fig. 1). Rapid extinction of the CAR took place in operated rats while extinction was delayed in the controls. The treatment with  $\alpha$ -MSH during extinction did not affect the rapid rate of extinction of the CAR of rats bearing lesions in the parafascicular thalamic area. The number of CAR's in the placebo-treated rats with lesions amounted to  $57.1 \pm 2.6$  and to  $127.4 \pm 2.5$  in sham-operated controls while the appropriate value for the  $\alpha$ -MSH treated rats was  $66.8 \pm 8.0$ . The difference between sham-operated and operated groups was significant at the 0.001 level.

Histological verification of the lesions showed a complete destruction of the parafascicular nucleus of the thalamus on both sides sometimes extending to the most medial part of

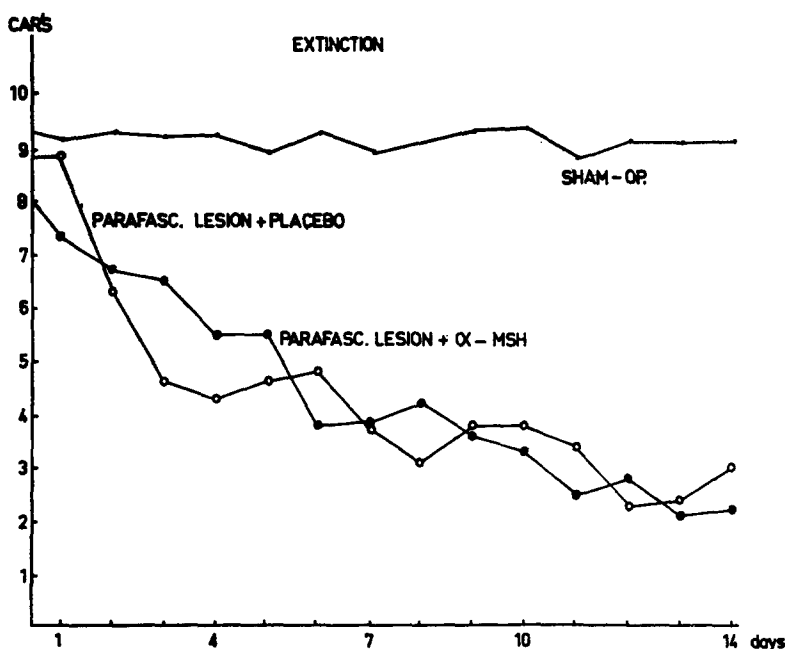


FIG. 1. Effect of  $\alpha$ -MSH or placebo on extinction of an avoidance response in rats with lesions in the nucleus parafascicularis of the thalamus.

Final evaluation of the results was carried out after histological verification of the placement of the lesion.

The number of CAR's served as an index of avoidance behavior of each rat. Significant differences between groups were calculated with the aid of Student's *t*-test.

#### RESULTS

The number of rats which did not reach the criterion of learning within one hundred and forty trials for the group with the bilateral lesions was virtually the same as for the sham-operated animals: four out of thirty-three and three out of seventeen respectively. These "non-learners" were omitted from subsequent experiments.

Acquisition of the CAR did not differ among the three groups of animals. The number of conditioned responses (Mean  $\pm$  S.E.) amounted to  $105.7 \pm 1.5$  and to  $103.8 \pm 2.3$

the nucleus ventralis thalami or to the fasciculus retroflexus.

#### DISCUSSION

Recent observations on behavioral effects of hormones of pituitary origin stress the importance of ACTH, or ACTH-like peptides or Antidiuretic Hormone (ADH) in the course of avoidance behavior. Murphy and Miller [17] as well as Miller and Ogawa [16] reported that administration of ACTH during avoidance conditioning resulted in a delay of extinction in both intact and adrenalectomized rats. Observations from this laboratory also suggest that the behavioral effect of ACTH is independent of its action on the adrenals since ACTH-like peptides as  $\alpha$ -,  $\beta$ -MSH and ACTH 1-10 were found to delay extinction of a conditioned avoidance response [4, 9]. Removal of the posterior lobe of the pituitary, on the other hand, has been found to facilitate extinction of a

conditioned avoidance response. However, avoidance behavior can be maintained by the administration of long-acting ACTH,  $\alpha$ -MSH or pitressin in the posterior lobectomized rat [8].

The present observations demonstrate that the effect of  $\alpha$ -MSH is prevented by bilateral lesions in the thalamic parafascicular area. This finding indicates that the effect of peptides of pituitary origin on avoidance behavior manifests itself in the CNS. Central nervous effects of pituitary peptides have been reported by others. Krivoy and Guillemin [13] found neurotropic activity of  $\beta$ -MSH and Ferrari [10] showed that ACTH and  $\alpha$ -MSH given intracisternally evoked a stretching syndrome in dogs and rabbits.

The question arises whether the thalamic parafascicular region is the site of action of the pituitary peptides or whether higher nervous structures disrupted by the lesion, are involved. Observations in rats with thalamic reticular lesions suggest

that certain motivational deficits might be responsible for the rapid extinction of the avoidance response (Bohus and De Wied, in preparation). According to this suggestion the effect of  $\alpha$ -MSH might manifest itself through those mechanisms which subserve the organization of motivational factors in an avoidance situation.

Cardo and Valade [6] reported that impairments in avoidance behavior of rats bearing thalamic parafascicular nuclei lesions can be partially normalized by the administration of amphetamine. The failure of  $\alpha$ -MSH to affect the rate of extinction in rats with thalamic parafascicular lesions may suggest that the effect of pituitary peptides on avoidance behavior is of a more specific character than mere excitation of central nervous activity. This is in accord with observations in a so-called Open Field test in which no effect of ACTH-like peptides could be demonstrated [4].

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