Physiology and Behavior. Vol. 5, pp. 143–146. Pergamon Press, 1970. Printed in Great Britain

Effects of Hypophysectomy and $ACTH_{1-10}$ on Responsiveness to Electric Shock in Rats

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(Received 22 September 1969)

GISPEN, W. H., TJ. B. VAN WIMERSMA GREIDANUS AND D. DE WIED. *Effects of hypophysectomy and $ACTH_{1-10}$ treatment on responsiveness to electric shock in rats.* PHYSIOL. BEHAV. 5 (2) 143–146, 1970.—Response behavior of rats to unescapable electric shock was studied in intact and hypophysectomized animals. The threshold for flinch, jerk, run and jump was significantly lowered in hypophysectomized rats as compared to that of intact controls. Treatment with the ACTH analogue $ACTH_{1-10}$ did not affect threshold levels in hypophysectomized nor in intact rats. It is concluded that the stimulating effect of $ACTH_{1-10}$ on conditioned avoidance acquisition in hypophysectomized rats is not caused by an influence on sensory capacities.

Hypophysectomy $ACTH_{1-10}$ Electric shock Flinch Jerk Run Jump

THE PITUITARY–ADRENAL system seems to play an essential role in conditioned avoidance behavior. Several reports have demonstrated a decrease in acquisition rate of an avoidance respone following hypophysectomy [9]. Adrenocorticotrophic Hormone (ACTH) as well as its analogues—$ACTH_{1-10}$ and $ACTH_{4-10}$—are able to restore this acquisition rate to practically normal in hypophysectomized rats [9]. Since the analogues have no intrinsic corticotrophic activity the effect of ACTH is not directed towards the adrenal cortex, but is probably an extra target effect. The decreased response performance following hypophysectomy might be the result of failing motor and or sensory capacities of the hypophysectomized organism. However, the decreased motor capacity of hypophysectomized rats, as assessed in runway experiments is only slightly restored by treatment with an ACTH analogue [9]. The runway only partly informs about the sensory capacities of the hypophysectomized rat. Accordingly these capacities were studied by measuring electric shock threshold levels in hypophysectomized rats in comparison to those of intact control animals. In addition the effect of treatment with an ACTH analogue on these electric shock threshold levels was studied in hypophysectomized as well as in intact rats.

MATERIALS AND METHODS

Male albino rats of an inbred Wistar strain, weighing 110–120 g, were used. Hypophysectomy was performed via the transauricular route under light ether anesthesia. Hypophysectomized rats were used three weeks after surgery. Unoperated control rats were of the same weight. Loss of body weight, adrenal and testes atrophy, thymus weight and macroscopic inspection of the sella turcica at the end of the experiment were indications that hypophysectomy had been correctly performed. In addition, plasma corticosterone levels, measured according to Van der Vies *et al.* [7] using a slightly modified technique, served as a parameter for hypophysectomy and the treatment of $ACTH_{1-10}$ on adrenocortical activity.

$ACTH_{1-10}$ was prepared as a long acting Zn–phosphate complex [8]. Placebo and $ACTH_{1-10}$ (20 μg/0.5 ml) were injected subcutaneously every other day during the last 10 days before the behavioral sessions.

Response behavior to electric shock was studied in a rectangular perspex box (40 × 40 × 35 cm) equipped with a stainless steel grid floor (inter bar distance: 1 cm). The box was illuminated during the test by a 100 W bulb placed on top of the box. Foot shock was applied by a 540 V (a.c.) shock source with a stepwise variable series resistor. The resistance of the rat is low in comparison to that of the shock source.

All animals were habituated to the box for a period of 5 min the day prior to testing. A modified method of limits as described by Turner *et al.* [6] was used. Three sets consisting of 11 shock intensities were presented 2.5 hr apart. The short circuit values of the intensities used were in mA: 0.033, 0.042, 0.058, 0.093, 0.107, 0.125, 0.157, 0.173, 0.216, 0.250 and 0.300. Each shock lasted 1 sec and the interval between the shocks was 30 sec. The shock intensities in the first set were presented in an ascending order, those of the second set in a descending order and those in the last set in a fixed random sequence.

Following each shock a response was recorded. The responses observed were defined as follows

A. "*No response*"

Indicating no detectable responses to shock.

B. "*Flinch*"

This response was interpreted as a sudden startled movement in which the animal's feet did not leave the grid.

C. *"Jerk, Run and Jump" Response*

The jerk was defined as a violent and sudden movement of the body. The run is a movement of the animal forward or backward more than 3/4 of its own body length. Jump is a response in which all four feet left the grid simultaneously.

The shock threshold for a response was calculated as the mean of the lowest intensities to which the rat, in the 3 shock series, performed the response. At the end of the shock series, the rats were sacrificed by decapitation.

RESULTS

As can be seen from Table 1 hypophysectomy had been performed correctly and $ACTH_{1-10}$ treatment had no detectable effect on any of the endocrine parameters measured.

The data from the shock tests show that the threshold for flinch responses was significantly lowered following hypophysectomy (Table 2). The difference in mean values between intact and hypophysectomized rats amounted to 0.050 mA. This value represents a decrease of more than 50 per cent in flinch threshold level. No significant change in this level was found following treatment with $ACTH_{1-10}$ either in unoperated control rats or in hypophysectomized animals in comparison to placebo treatment.

Jerk, run and jump threshold of hypophysectomized rats was also significantly lowered (Table 2). The difference amounted to 0.026 mA indicating a decrease of approximately 25 per cent. Again, no significant change in mean threshold value was found following $ACTH_{1-10}$ treatment.

As can be seen from Table 3, the number of scored "no response" was significantly decreased in the hypophysectomized group. This decrease in "no response" scores is accompanied by an increase in flinch and jerk, run and jump responses as compared to that of control animals. This indicates that hypophysectomized rats are more susceptible to electric shock than controls.

TABLE 1

EFFECTS OF HYPOPHYSECTOMY AND ACTH $_{1-10}$ ON BODY WEIGHT AND ENDOCRINE PARAMETERS

	Number of Rats	Change in Body Weight (g)	Thymus Weight (mg)	Testes Weight (mg)	Adrenal Weight (mg)	Plasma Corticosterone (μg/100 ml)
Control + Placebo	6	+38 ± 1.8*	356 ± 28	2182 ± 66	28.5 ± 1.3	26.1 ± 3.6
Control + $ACTH_{1-10}$	6	+40 ± 1.7	321 ± 17	2246 ± 55	27.2 ± 1.3	24.4 ± 2.0
Hypox† + Placebo	6	−17 ± 1.1	134 ± 22	291 ± 15	7.55 ± 0.55	2.5 ± 0.3
Hypox + $ACTH_{1-10}$	6	−18 ± 1.0	134 ± 14	341 ± 41	7.03 ± 0.35	3.8 ± 0.7

*Mean ± Standard Error of the Mean.
†Hypox = Hypophysectomized.

TABLE 2

RESPONSE THRESHOLD VALUES TO ELECTRIC SHOCK

	Number of Rats	Flinch (mA)		Jerk, Run and Jump (mA)	
Control + Placebo	6	0.093 ± 0.0066	*	0.123 ± 0.0073	
Control + ACTH $_{1-10}$	6	0.084 ± 0.0069	‡	0.122 ± 0.0118	§
Hypox†+ Placebo	6	0.043 ± 0.0038	‡	0.097 ± 0.0079	
Hypox + ACTH $_{1-10}$	6	0.043 ± 0.0028		0.091 ± 0.0076	

*Mean ± Standard Error of the Mean.
†Hypox = Hypophysectomized.
‡$p \leq 0.01$ (two-tailed modified *t*-test).
§$p \leq 0.05$ (two-tailed modified *t*-test).

TABLE 3

NUMBER OF SCORED RESPONSES OUT OF 33 TRIALS PER RAT

	Number of Rats	No Response	Flinch	Jerk, Run and Jump
Control + Placebo	6	10.5 ± 1.2 *	4.2 ± 0.8	18.3 ± 1.1
Control + $ACTH_{1-10}$	6	9.3 ± 0.3 ‡	5.0 ± 1.0 §	18.7 ± 1.4
Hypox† + Placebo	6	3.2 ± 1.0 ‡	8.2 ± 1.1	21.7 ± 1.3 §
Hypox + $ACTH_{1-10}$	6	3.0 ± 0.4	6.8 ± 0.5	23.2 ± 0.8

*Mean ± Standard Error of the Mean.
†Hypox = Hypophysectomized.
‡$p \leq 0.01$ (two-tailed modified t-test).
§$p \leq 0.05$ (two-tailed modified t-test).

DISCUSSION

Although it had been reported that flinch responses occur at all shock intensities [3, 10], the present results show that flinch responses occur only in the region of low shock intensities (Table 2, Fig. 1). An increase in shock intensity is followed by an increase in the number of jerk, run and jump responses. The same relationship between shock intensity and response behavior has also been found by Kimble [4], Evans [1] and Turner and coworkers [6]. Hypophysectomy significantly lowered the threshold levels for the various responses to shock. This decrease in threshold level was accompanied by a significant decrease in the number of occasions in which no response was recorded. In view of this, it can be concluded that hypophysectomy increases the sensitivity of rats to electric shock stimuli. It is of interest to note, that an increased sensitivity to electric shock has been observed also in rats with lesions in the ventromedial hypothalamus [6] and in the median forebrain bundle [5, 7].

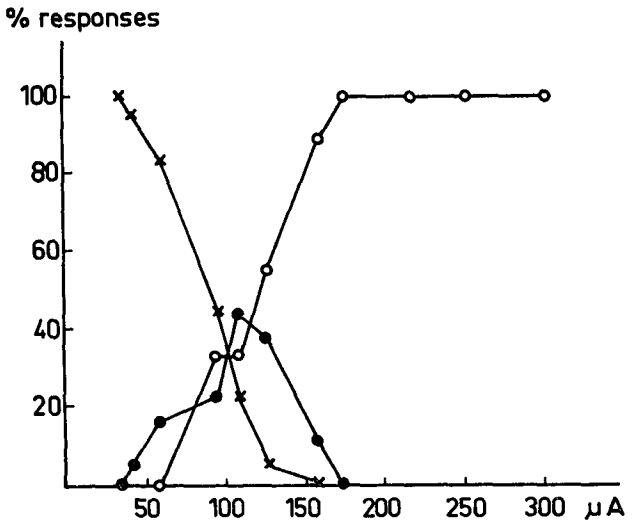

FIG. 1. Relationship between shock intensity and responses scored in placebo treated control rats.
x —— x no response
● —— ● flinch
○ —— ○ jerk, run and jump

Hypophysectomized rats show defective learning of conditioned avoidance [9]. However, when responding to electric shock their threshold levels are significantly lowered. These paradoxal results contrast with the view that response to electric shock is an important determinant in avoidance behavior [3, 4]. However, they are in agreement with the studies of Wilcock [10, 11], who suggested that avoidance performance is not closely correlated with the animals' response to electric shock.

No influence of the ACTH analogue $ACTH_{1-10}$ on electric shock threshold levels could be demonstrated in hypophysectomized or control rats. Thus the stimulating effect of $ACTH_{1-10}$ on avoidance acquisition in hypophysectomized rats is not the result of an influence on response behavior to electric shock. The sensory capacities of hypophysectomized animals appeared to be even better than those of intact rats. The marked restoration of the rate of avoidance acquisition of hypophysectomized rats by treatment with ACTH and with an ACTH analogue like $ACTH_{1-10}$ therefore can not be explained by an effect on sensory capacities.

We gratefully acknowledge the generous supply of $ACTH_{1-10}$ by N.V. Organon, Oss, Holland.

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