Reports

Adrenocorticotropin Secretion Inhibited by Implantation of Hydrocortisone in the Hypothalamus

Abstract. Small quantities of crystalline hydrocortisone acetate, when implanted stereotaxically into the hypothalamus of rats, resulted in inhibition of compensatory adrenal hypertrophy and in adrenal atrophy. Similar implants of hydrocortisone in the pituitary gland, and of cholesterol in the hypothalamus, had no noticeable effect on the adrenals.

The importance of the central nervous system and particularly the hypothalamus in the control of adrenocorticotropin (ACTH) secretion is generally agreed upon (*1*). There is, however, much less certainty about the participation of the brain in the so-called "feedback" regulation of this hormone, whereby fluctuations in the blood level of adrenocortical hormones modify ACTH output. It has been shown, in dogs and rats with lesions in the hypothalamic median eminence, that decreases in peripheral corticoid levels fail to provoke increases in ACTH secretion (*2*). On the other hand, the available evidence suggests that augmented blood levels of corticoids do not act at the level of the hypothalamus (*2*), but either directly on the pituitary gland or at some other unknown locus.

Previous studies (*3*) have indicated that intracerebral implants of small quantities of crystalline steroid hormones can exert specific effects on localized areas of the brain, and that systemic hydrocortisone affects evoked potentials in the hypothalamus (*4*). Our experiments were conducted to study the effects of the local implantation of crystalline hydrocortisone in the hypothalamus and pituitary on ACTH secretion.

Forty adult, male albino rats were used. The right adrenal was removed at the beginning of the experiment, the left one 9 days later. In eight rats with unilateral adrenalectomy, the mean difference in adrenal weight [(left adrenal weight minus right adrenal weight × 100) divided by right adrenal weight] was +53.9 ± 7.2 percent (standard error). This "compensatory hypertrophy" presumably results from the increased ACTH secretion attendant upon a decrease in corticoid titer of the blood.

Thirty-two other rats received, at the time of unilateral adrenalectomy, implants of small quantities (about 0.2 mg) of crystalline hydrocortisone acetate or cholesterol. These substances were introduced into the brain by 20-gauge stainless steel tubing implanted with a stereotaxic instrument and fixed to the rats' skulls with dental cement. As all implants were made either into the base of the hypothalamus or into the pituitary, it was possible to verify their locations by direct visualization of the base of the brain at autopsy, when a clearly recognizable white spot of material could be seen.

Nineteen rats received hydrocortisone implants in the hypothalamus. In 11 of these rats (Fig. 1, group A) compensatory adrenal hypertrophy was absent. In each case the left adrenal was significantly smaller than the right one, a situation very seldom encountered in unoperated normal rats. The hormone in all of these animals was deposited in the sagittal plane of the brain, in nine cases in the median eminence, and in two cases in the mammillary body. The mean difference in adrenal weight was −19.6 ± 2.1 percent (range −7.4 to −28.0 percent). Histologically, these adrenals showed shrinkage of the inner layers of the cortex and an apparent hypertrophy of the zona glomerulosa similar to that noted in hypophysectomized rats (*5*).

In another group of eight rats (Fig. 1, group B) no adrenocortical atrophy resulted from hydrocortisone implantation, but partial inhibition of compensatory hypertrophy apparently occurred. The mean difference in adrenal weight was +28.2 ± 3.2 percent. In one of these animals the implant was located at the lateral limit of, and just outside, the hypothalamus, and the weight difference was +44.8 percent. In three, implants were in the lateral hypothalamus, in three, in the mammillary body, and in one there was an implant unilaterally impinging on the median eminence. The adrenal weight differences in these seven rats ranged from +15 to +35.4 percent.

In contrast to these, the implantation of hydrocortisone directly into the pituitary glands of five rats did not yield any noticeable effect on the weight or histology of the adrenals. The mean difference in adrenal weight in these animals was +64.2 ± 8.2 percent.

To test the possibility that the inhibitory effect of hypothalamic implants might be due to a lesion produced mechanically by the insertion of the hormone, cholesterol was similarly implanted into the median eminence region in eight rats. In these animals the response to unilateral adrenalectomy was completely normal, the mean difference in adrenal weight being +58.3 ± 6.3 percent.

Although the quantities of hydro-

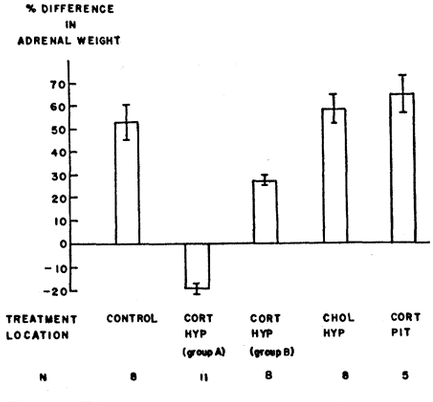

Fig. 1. Effects of intracranial implantation of hydrocortisone acetate and cholesterol on adrenal compensatory hypertrophy. Abbreviations: CORT, hydrocortisone acetate; HYP, hypothalamus; CHOL, cholesterol; PIT, pituitary. In group A, implants were in the midline, and in group B they were placed laterally or in the mammillary region. Small bars above and below means are standard errors of the mean.

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper.

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to contributors" [*Science* **125**, 16 (1957)].

cortisone implanted varied somewhat from animal to animal, unabsorbed material was invariably observed at autopsy, and there was no correlation between the degree of inhibition following intrahypothalamic implantation and the quantity of hydrocortisone introduced. In most rats bearing pituitary implants more hydrocortisone was used than for animals that were implanted with hydrocortisone in the hypothalamus, and in the case of intrahypothalamic cholesterol implants, even larger amounts of this substance were utilized.

While this study was in progress, Endroczi *et al.* (*6*) reported that intracerebral injections of cortisone acetate in cats and rats inhibited acute stress-induced increases in adrenal venous corticoids when these injections were made into the ventral hypothalamus, or to a lesser extent into the midbrain. Since the hormone they injected spread over a considerable area, they concluded that the cortisone in the case of the hypothalamic injections had diffused to the pituitary and acted there. Our investigation, however, shows that hydrocortisone, when implanted directly into the pituitary, does not interfere with compensatory hypertrophy of the adrenal cortex after unilateral adrenalectomy, while similar implants into the hypothalamus result in adrenal atrophy. The fact that cholesterol implantation in the median eminence was ineffective suggests that our results indicate a specific inhibitory effect of hydrocortisone on an ACTH-regulating "center" in the hypothalamus (*7*).

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References and Notes

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7. This investigation was supported wholly by grant No. 244 from the National Multiple Sclerosis Society. The hydrocortisone acetate was supplied by Teva Pharmaceutical Co.

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Higher Nervous Activity in Cats with Midpontine Pretrigeminal Transections

Abstract. In cats with midpontine pretrigeminal transections, orientation reflexes to visual stimuli consist only of vertical eye movements, pupillary dilation, and electroencephalographic arousal. Extinction of the orientation reflex by repetition of the photic stimulus is easily obtained; the reflex partially recovers after a few minutes of rest. By using as reinforcement stimulation of hypothalamus producing pupillary dilation and EEG arousal, conditioned responses to a visual stimulus may be obtained. The cat with midpontine pretrigeminal transection can be used as convenient preparation for the study of the orientation and conditioned reflexes.

Recent experiments (*1*) have shown that pontine transections in the cat, rostral to the entrance of the trigeminal nerve, are followed by low-voltage fast activity in the electroencephalogram (EEG). In the pretrigeminal transected animals, eye movements and pupillary dilation in response to visual stimuli were also observed. In the experiments reported here, orientation reflexes and conditioning were studied in the same preparation.

Only cats which breathed spontaneously and demonstrated good phasic reflexes and extensor rigidity were selected. Some animals showed permanent EEG sleep patterns, indicating that the level of the transection was too high. These animals were rejected. After undergoing surgery, the cat, still in the stereotaxic instrument, was placed in a small chamber. The background illumination was continuous. Pupils were constricted to a transverse diameter of about 1 mm. Two visual stimuli were used: a train of flashes and a rotating object. The strong background illumination produced fissurated miosis, so that no photic reflex to the train of flashes could be detected. Both stimuli lasted 2 seconds. The train of flashes was the conditioned stimulus. The conditioned stimulus was reinforced by electrical stimulation of the central hypothalamus, producing strong pupillary dilation and EEG arousal (*2*).

Each experimental session consisted of 10 to 20 trials, with intertrial intervals of 1 to 2 minutes. The interval between the onset of the train of flashes and hypothalamic stimulation was about 0.5 second at the beginning, and was gradually increased to about 5 seconds. The intervals between sessions were from 1 to 3 hours; however, after several sessions an 8-hour interval was always introduced. In some cats which remained in good condition for 3 or 4 days a number of sessions were conducted.

When the rotating object was presented for the first time, it usually produced a strong reaction, consisting of pupillary dilation (Fig. 1) and eye movement towards the stimulus. If the stimulus was given during EEG synchronization a desynchronization was also observed. The train of flashes produced a similar reaction, but it was always much weaker and sometimes absent. When the visual stimulus was applied repeatedly with short intervals (1 to 2 minutes) the reaction rapidly disappeared. The reaction reappeared spontaneously, however, after a period of rest of 5 to 10 minutes. This type of reaction, with rapid habituation and spontaneous recovery, suggests that we are concerned here with the ocular components of the orientation reflex.

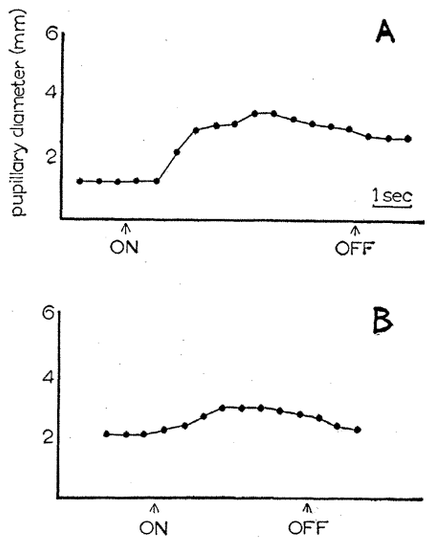

Fig. 1. Pupillary responses to rotor (*A*) and train of flashes (*B*).

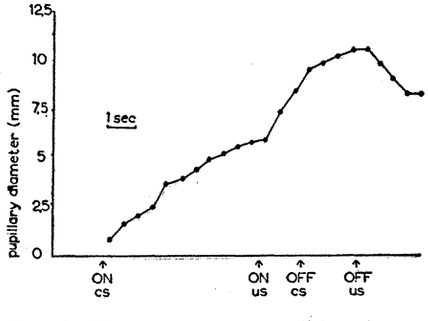

Fig. 2. Elaboration of conditioned mydriasis to the trains of flashes. Strong pupillary dilation to the train of flashes in the first trial of the 11th experimental session.