Effect of Synthetic Vasopressin on Release of Adrenocorticotrophin in Rats with Hypothalamic Lesions.* (23541)

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The hypothesis that the antidiuretic hormone (ADH) regulates the release of adrenocorticotrophin (ACTH) from the adenohypophysis is supported by the following evidence: i) ADH and ACTH are released under similar circumstances(1). ii) A defect in ACTH release is correlated with diabetes insipidus in rats with hypothalamic lesions(2). iii) Pitressin, a commercial extract containing the pressor-antidiuretic activity of the posterior lobe, releases ACTH in rats with lesions which block the release of ACTH to a variety of non-specific stimuli(2,3). iv) There is a correlation between pressor and ACTH-releasing activity of posterior lobe extracts, suggesting that ACTH-releasing activity may be a property of the pressor-antidiuretic hormone(3). Extracts of the posterior lobe having pressor activity appear to release ACTH from the pituitary also *in vitro*, but a similar activity has been obtained from extracts possessing little or no pressor activity(4,5). Therefore, in the present experiments the ACTH-releasing activity of synthetic vasopressin† has been evaluated as a further test of the hypothesis that the neurohumor stimulating the release of ACTH is vasopressin itself.

In these experiments rats with acute hypothalamic lesions were used as assay animals since it has been shown that these rats do not respond to a variety of non-specific stimuli while retaining their response to ACTH(1). Hence, it has been assumed that these lesions block the pituitary-adrenal stress response at the hypothalamic level and that the animals should respond to the presumed neurohumor which evokes the secretion of ACTH.

Methods. Hypothalamic lesions were placed in the median eminence of the tuber cinereum of male Wistar rats (270-330 g) as previously described(3). Those animals with water intakes in excess of 110 ml in the first 24 hours after the operation were used for assay 24 hours later (*i.e.* 48 hr post-op), providing they appeared to be in good condition. Adrenal ascorbic acid depletion was used as the index of ACTH release in all experiments. The left adrenal was removed under ether anesthesia to obtain a control value for adrenal ascorbic acid. One hour after unilateral adrenalectomy or injection of a test drug, the second gland was removed for analysis(3).

Results. The rats with hypothalamic lesions showed no response to unilateral adrenalectomy alone (Table I). In contrast, both Pitressin and synthetic vasopressin elicited a significant ascorbic acid depletion (Table I, Fig. 1). The responses to the 2 drugs were indistinguishable when dosage was expressed in pressor units. The minimal effective dose of both preparations was of the order of 0.1 International Unit (U). On assay at varying dosages, Pitressin exhibited a potency 83% that of synthetic vasopressin, considering the synthetic material the standard at 100%. The 95% confidence limits of the assay were 32-219%.‡

Thus, these results clearly show that synthetic vasopressin can release ACTH in this experimental situation. It seems highly likely, then, that the vasopressin molecule itself possesses intrinsic activity in the release of ACTH. The activity of commercial Pitressin in releasing ACTH in these experiments can be entirely accounted for by its content of vasopressin. Therefore, there seems no need to postulate that a contaminant with significant ACTH releasing action is present in posterior lobe extracts in the doses employed. Ten U of Pitocin, a commercial preparation of

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‡ Calculated by the method of Irwin (see Pugsley, L. I., *Endocrinol.*, 1946, v39, 161).

TABLE I. Comparison of ACTH-Releasing Activity of Pitressin with That of Synthetic Lysine-Vasopressin in Rats with Acute Hypothalamic Lesions.

Treatment	No. of rats	Adrenal ascorbic acid depletion (mg/100 g adrenal) Mean ± S.E.	Individual responses
1. Control*	6	−6 ± 8	−2, −4, 12, 10, −42, −10
2. Pitressin			
5 U†	3	158	116, 199, 160
.5 U	6	96 ± 19	108, 141, 147, 18, 80, 80
.25 U	5	74 ± 14	104, 31, 86, 49, 98
.1 U	4	36 ± 19	13, 15, 23, 94
3. Lysine-vasopressin			
1.0 U	7	125 ± 30	112, 258, 123, 54, 130, 67, 161
.5 U	6	77 ± 21	27, 55, 148, 131, 72, 28
.25 U	6	77 ± 19	147, 20, 83, 34, 102, 79
.12 U	7	55 ± 21	14, −6, 30, 94, 89, 140, 27
.062 U	5	31 ± 7	37, 17, 27, 17, 55
4. Pitocin			
10 U	7	44 ± 18	2, 64, 50, −13, 10, 90, 115

* Unilateral adrenalectomy only; all other animals were inj. with the drug to be tested immediately after unilateral adrenalectomy.

† All inj. given intrav. during a period of 3 min.

the oxytocic hormone, evoked no significant ACTH release ($P<0.1>0.05$). Since this dose is approximately 100 times the minimal effective dose of vasopressin, it appears that oxytocin plays little or no role in the release of ACTH.

Because of the failure of these rats with lesions to respond to a variety of non-specific stimuli, it appears reasonable to assume that the action of vasopressin in these experiments is directly on the adenohypophysis. The large dose of vasopressin required to release ACTH in these experiments suggests that if vasopressin is to act as the ACTH-releasing neurohumor, it would need to be released into the hypophyseal portal vessels so as to reach the adenohypophysis in a relatively high concentration.

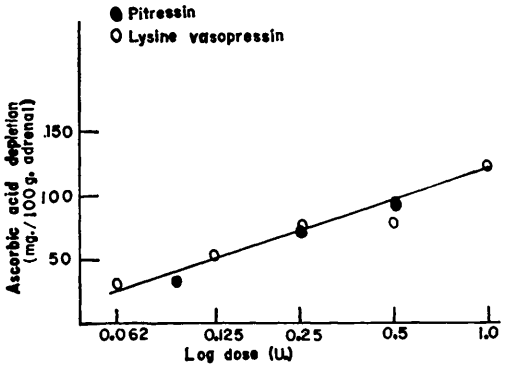

FIG. 1. Activity of posterior lobe extracts.

Conclusions. Commercial and synthetic vasopressin are equipotent in producing ascorbic acid depletion in rats with those hypothalamic lesions which prevent the adrenal response to certain non-specific stimuli. The results are interpreted to mean that vasopressin can evoke ACTH release in these animals and that the ACTH-releasing activity of neurohypophyseal extracts, when tested *in vivo*, is accounted for by their content of vasopressin. The results support the hypothesis that vasopressin (ADH) is the neurohumor responsible for ACTH release.

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