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Vago-Neurohypophysial Pressor Reflex.

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It has been shown repeatedly that interruption of the supraoptico-hypophysial tract causes atrophy of the neurohypophysis with certain cellular alterations. If sufficient neurohypophysis is deprived of its nerve supply in this way, diabetes insipidus ensues (Fisher, Ingram and Ranson[1]). These atrophic neurohypophyses have been found to be lacking in the hormonal substances produced by the normal gland, and it is generally held that diabetes insipidus is due to lack of an antidiuretic hormone. The question remains, is the innervation of the neurohypophysis a trophic one, or may it participate in the regulation of the functions of the latter? There is some evidence for neurogenic control of the neurohypophysis.

Theobald and Verney,[2] and Pickford[3] have advanced indirect evidence to show that humoral and neural influences may cause the neurohypophysis to increase its output of antidiuretic substance. Haterius[4] has confirmed this and added more direct evidence for participation by the pituitary. Gilman and Goodman[5] found antidiuretic substance in the urine of dehydrated normal rats, as did Boylston and Ivy,[6] the latter pointing out the similarity between the action of this antidiuretic substance and that of pitressin. Gilman and Goodman could not obtain similar results with dehydrated hypophysectomized rats. Ingram, Ladd and Benbow[7] have offered evidence that while appreciable amounts of antidiuretic substance are excreted by normal cats in a state of dehydration, dehydrated cats with diabetes insipidus do not excrete such material. Walker,[8] however, did not obtain such results. Gersh[9] reports that "paren-

1 Fisher, C., Ingram, W. R., and Ranson, S. W., *Diabetes Insipidus*, Edwards Brothers, Inc., 1938.

2 Theobald, G. W., and Verney, E. B., *J. Physiol.*, 1935, **83**, 341.

3 Pickford, M., *J. Physiol.*, 1939, **95**, 226.

4 Haterius, H. O., *Am. J. Physiol.*, 1940, **128**, 506.

5 Gilman, A., and Goodman, L. S., *J. Physiol.*, 1937, **90**, 113.

6 Boylston, C. A., and Ivy, A. C., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 644.

7 Ingram, W. R., Ladd, L., and Benbow, J. T., *Am. J. Physiol.*, 1939, **127**, 544.

8 Walker, A. M., *Am. J. Physiol.*, 1939, **127**, 519.

9 Gersh, I., *Am. J. Anat.*, 1939, **64**, 407.

chymatous glandular cells" of the neurohypophysis of rats increase in size and number in dehydration and at parturition.

Chang, Lim, *et al.*,[10, 11] have reported a series of interesting observations made upon experimental animals in which the only connection between head and body was vascular. Stimulation of the central end of the cut vagus in such dogs caused characteristic elevations of blood pressure. Since acute hypophysectomy abolished this response, they ascribed this reflex to a liberation of a pressor principle from the neurohypophysis, indicating that the integrity of the reflex arc depended upon the presence of an intact supraoptico-hypophysial tract and anatomically obscure central intermediary neurons. In similar experiments increased production of oxytocic, glucogenic and antidiuretic substances was also described. These results are of such significance as to warrant confirmation. This communication deals with an attempt to confirm certain findings of these workers, and with further data from experiments carried out on dogs with chronically denervated neurohypophyses. The latter experiments were designed to rule out errors which may conceivably be introduced by the trauma and shock contingent upon acute hypophysectomy.

Methods. In all experiments nembutal anesthesia was given intravenously. Blood pressure was recorded from the femoral artery. After isolation of the carotids, jugulars, and vagi, and cannulation of the trachea, all other neck structures were crushed in a specially constructed vise according to the methods of Chang, *et al.* The artificial respiration rate was 8 respirations per minute. The blood pressure fall consequent to cord crushing was combated by the intravenous administration of Ringer's solution and 5 mg doses of ephedrine. By these means it was found possible to maintain the blood pressure at or above 70 mm Hg; experiments in which the basal pressure was lower than this level were discarded. Destruction of the spinal cord was checked at autopsy.

Results. 1. *Acute experiments.* After the technic of preparing such an animal was sufficiently developed, it was found that the rise in blood pressure on stimulation of the central end of the severed vagus was quite easily obtainable. In these experiments, acute hypophysectomy was carried out through an opening in the roof of the mouth so as not to disturb other intracranial structures. The

[10] Chang, H. C., Chia, K. F., Hsu, C. H., and Lim, R. K. S., *Chin. J. Physiol.*, 1937, **12**, 309.

[11] Chang, H. C., Lim, R. K. S., Lu, Y. M., Wang, C. C., and Wang, K. J., *Chin. J. Physiol.*, 1938, **13**, 269.

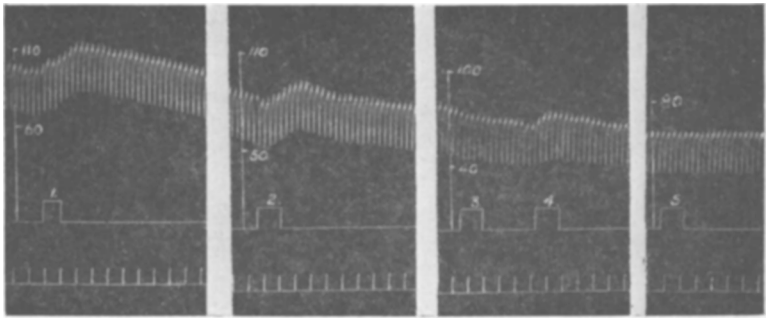

FIG. 1.
Blood pressure tracings from a dog with the cervical spinal cord crushed. Responses to stimulation of the central vagus stump, with the effect of cervical sympathetic ganglionectomy and hypophysectomy.

completeness of posterior lobe resection was confirmed by careful autopsy examination.

The results of a typical experiment are illustrated in Fig. 1. At 1, faradic stimulation (coil at 5 cm) of the left vago-sympathetic trunk for 45 sec. Note the sudden pressor effect upon which a second mild pressor phase is superimposed. Between 1 and 2 the left superior cervical sympathetic ganglion was removed. At 2, stimulation of the central end of the left vagus for 45 seconds. After a 30-second delay a rise in pressure occurs. Between 2 and 3 the hypophysis was removed through a previously made opening in the roof of the mouth. At 3, stimulation of the central end of the left vagus for 45 seconds. No response. At 4, the intact right vago-sympathetic trunk was stimulated for 45 seconds. Sudden onset of pressor response. Between 4 and 5 the right superior cervical sympathetic ganglion was removed. At 5, stimulation of the right vagus caused no response in blood pressure. Such results were obtained in 7 experiments.

Conclusions. In a normal dog, with the spinal cord crushed, stimulation of the central end of the vago-sympathetic trunk causes a pressor effect in the body. This effect seems to be of two components; a sudden rise (sympathetic effect) and a more delayed rise (vagus-neurohypophysis effect). That the elevated pressure resulting from stimulation of the vagus alone is effected through the pituitary is indicated by abolition of the response through hypophysectomy.

This experiment was tried on several cats with similar results but with great variability under the conditions. Technical obstacles made the experiment difficult.

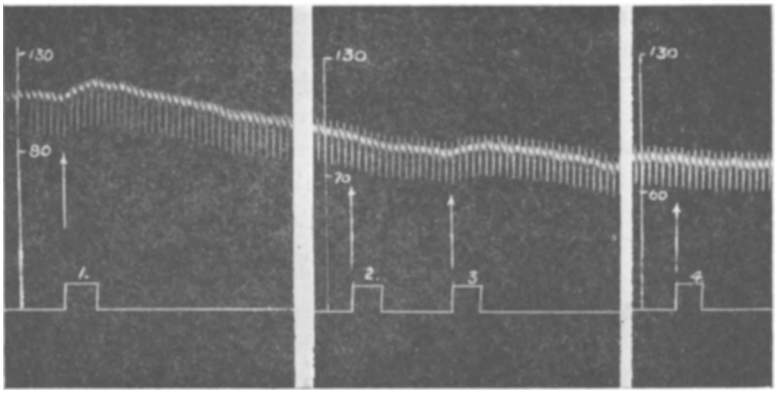

FIG. 2.
Blood pressure tracings from dog 14, with diabetes insipidus and the cervical spinal cord crushed. Responses to stimulation of the central vagus stump before and after cervical sympathetic ganglionectomy.

2. *Experiments with dogs with chronically denervated neurohypophyses.* In these animals the supraopticohypophysial tract was sectioned in the median eminence, using a subtemporal approach. Criteria for the completeness of the section were the occurrence of marked permanent diabetes insipidus and examination of microscopic sections of the infundibular region. These dogs were used to show further that the pressor response is abolished in the absence of neurohypophysial innervation, and to rule out any possible error caused by trauma and shock in the acutely hypophysectomized animals.

The following experiment is typical:

Dog No. 14. Before stalk section average urine output was 200 cc (Sp. Gr. 1.032). After section of the stalk average urine output was 2978 cc (Sp. Gr. 1.002). Following the 6th day there was a 4-day normal interphase after which the water intake and urine output rose to the previous high level. On the 16th postoperative day the spinal cord was crushed and stimulations were carried out (Fig. 2). At 1, faradic stimulation of the right vago-sympathetic trunk (coil at 5 cm) for 45 seconds. Immediate onset of a pressor effect. Between 1 and 2 the right superior cervical sympathetic ganglion was removed. At 2, stimulation of the right vagus for 45 seconds caused no change in blood pressure. At 3, stimulation of the left vago-sympathetic trunk for 45 seconds. Immediate pressor effect. Between 3 and 4 the left superior cervical sympathetic ganglion was removed. At 4, stimulation of the left vagus for 45 seconds caused no change in the blood pressure.

Similar results were obtained in 3 experiments. In addition a dog

with diabetes insipidus in which cervical sympathetic ganglionectomy was not done yielded only typical sympathetic responses without evidence of vagus pressor responses. In one operated dog with a good transient but not a permanent polyuria, vagoneurohypophysial responses were not obtained; microscopic sections showed extensive but not quite complete degeneration of the supraopticohypophysial system.

Conclusions. Stimulation of the central end of the vago-sympathetic trunk in a dog with diabetes insipidus gives a pressor response. This pressor response is due to stimulation of the sympathetics of the head, since the response is abolished by sympathetic ganglionectomy. In the absence of the supraopticohypophysial connection the vagus-postpituitary reflex is not obtainable even under the best conditions, as when the basal blood pressure level is high.

3. In a number of acute experiments the infundibulum was stimulated directly with weak faradic current. Fine bipolar electrodes were used and introduced manually through a buccal opening. The spinal cords were completely crushed in each of these dogs. Striking elevations in blood pressure were obtained. These experiments supplement those of Clark and Wang[12] in which hypothalamic stimulation produced pressor effects in spinal cats, and offer further indication that the results of these workers were due to activation of the neurohypophysis.

Summary. 1. In dogs with only vascular connections between head and body, stimulation of the central end of the severed vagus causes blood pressure elevations in the body. Acute hypophysectomy abolishes this reflex. 2. This reflex cannot be obtained in preparations with chronic diabetes insipidus caused by interruption of the supraopticohypophysial tract. This rules out possible error due to shock, trauma, etc., consequent to acute hypophysectomy. 3. These results add to the evidence found elsewhere that the neurohypophysis is subject to nervous control mediated by the supraopticohypophysial tract.

[12] Clark, G., and Wang, S. C., *Am. J. Physiol.*, 1939, **127**, 597.