THE REGULATION OF WATER EXCRETION BY THE NEUROHYPOPHYSIS*

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THE first experiments on the endocrine functions of the posterior pituitary were performed more than a half century ago by Oliver and Schäfer.[1] They described the marked vasopressor response to pituitary extracts which owed their effects to the posterior-lobe tissue. There was considerable confusion for a number of years with respect to the renal effects of posterior-pituitary extract owing to the restriction of experiments to intravenous injection of large doses of extract into anesthetized animals. The first clue concerning the characteristic and specific renal effect of posterior-pituitary extract was given by the clinical experiments of von den Velden[2] and of Farini[3] who both reported in 1913 that posterior-pituitary extracts can markedly inhibit diuresis. These observations were made on patients with diabetes insipidus. A host of later investigators studied the neurohypophysial control of water metabolism both in animals and in man. Our debt is particularly great to Ranson and his colleagues working in Chicago and to Verney working both in London and Cambridge. The best documented evidence that the posterior pituitary is an important gland of internal secretion is based upon its control of the renal excretion of water and it is this topic which will be discussed in this lecture. (A second important endocrine function of the gland is to cause milk-ejection in the lactating mammary gland. It is probable that without milk ejection the nursing young cannot secure adequate supplies of milk. The endocrine importance of the neurohypophysis in labor has not been established.)

ANATOMICAL ASPECTS

The posterior pituitary is only one part of a unit which should be

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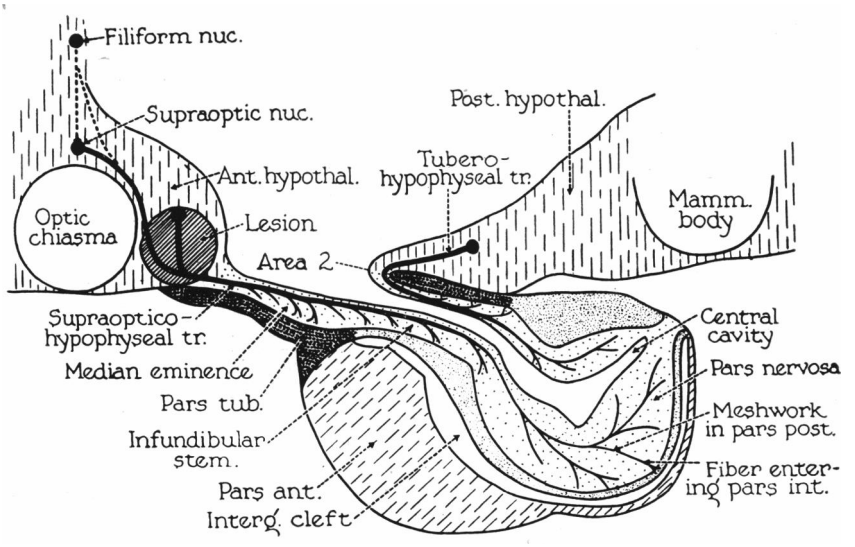

Fig. 1—Diagram of the hypothalamus and pituitary body of the cat (from Fisher, Ingram and Ranson *Diabetes insipidus*, 1938.[4] Reprinted by permission). Diabetes insipidus follows a lesion placed in the shaded circular area caudal to the optic chiasm.

designated the neurohypophysis.[4] The neurohypophysis consists of certain hypothalamic nuclei, their axons which traverse the stalk and the neural or posterior lobe of the pituitary in which the axons end (Figure 1). The stalk is sometimes called the infundibulum and the neural lobe, the infundibular process. The most important hypothalamic nuclei are the paired supraoptic nuclei; less important are the paraventricular nuclei and perhaps other groups of neurons which also supply axons to the stalk. These neurons are highly vascularized and differ morphologically from most normal neurons of the cerebrum; for example, they resemble neurons in which chromatolysis is progressing after section of their axons. Since about 1930, E. Scharrer and his colleagues have made many studies of the neurons of the supraoptic and related nuclei in a number of vertebrates; secretory granules peculiar to these neurons are characteristically present. In a recent communication Bargmann and Scharrer[5] recorded their belief that the secretory granules formed in the cells of supraoptic nuclei are transported in their axons in the stalk to the posterior pituitary where they are stored as the characteristic secretion of this lobe. Their illustration of neurosecretory granules in

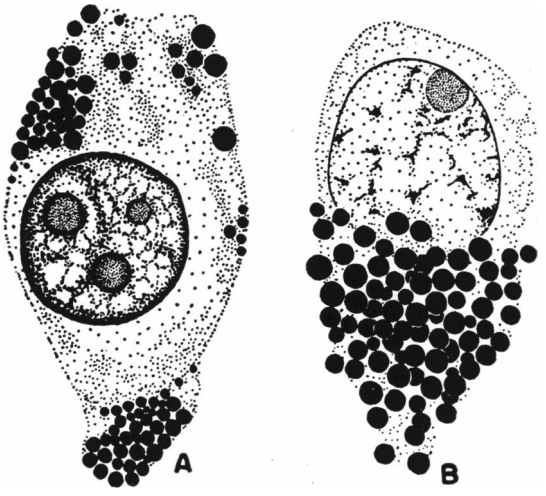

Fig. 2—Examples of neurosecretory cells in (A) the nucleus preopticus of the toad (*Bufo americanus*) and (B) the nucleus paraventricularis of the monkey (*Cebus capucinus*). (From Bargmann and Scharrer,[5] in *American Scientist 39*:255-59, 1951. Reprinted by permission).

cells of similar nuclei is reproduced in Figure 2. These nuclei contain more than 100,000 cells from which a corresponding number of axons sweep down the stalk to end in the neural lobe. The experiments of Ranson and his colleagues[4] demonstrated that diabetes insipidus could occur if there was an interruption of the tracts connecting the supraoptic and paraventricular nuclei with the neural lobe of the pituitary. If such an interruption is completed surgically the supraoptic neurons undergo degeneration, the posterior pituitary becomes atrophic and the syndrome of diabetes insipidus appears.

Physiological Considerations

Although Magnus and Schäfer[6] believed on the basis of their acute experiments in anesthetized animals that posterior-pituitary extracts are diuretic, the reverse was shown to be the case by von den Velden[2] and Farini[3] who injected extract into unanesthetized men with diabetes insipidus. Subsequent work has shown that the characteristic effect of extract is to inhibit water diuresis. This is accomplished by increasing the reabsorption of water by the kidney. Neurohypophysial secretion is the important hormonal means by which water is conserved in the

body and this hormone must be available if a mammal such as man has to excrete concentrated urine. H. W. Smith[7] has championed the view that the action of antidiuretic hormone is on the distal tubule. He points out that the tubular reabsorption of the water of the glomerular filtrate normally occurs by a passive or "obligatory" mechanism in the proximal tubule with respect to 85 to 90 per cent of the total volume filtered. The remaining 10 to 15 per cent is actively or "facultatively" reabsorbed in the distal tubule according to this view. Thus if there were a complete failure in the secretion of antidiuretic hormone the theoretical maximum diuresis could amount to 10 to 15 per cent of the total glomerular filtrate. A diuresis of this magnitude is rarely seen even in severe cases of diabetes insipidus; on the other hand, it is doubtful whether a complete deficiency of the secretion of the hormone ever occurs either in clinical diabetes insipidus or in its experimental counterpart.

The essential feature of the action of antidiuretic hormone is to increase the rate of reabsorption of water by the kidney. Much has been written concerning the effect of the hormone on electrolyte excretion. Although striking increases in electrolyte excretion may occur while the hormone is exerting an antidiuretic effect, an increased excretion of chloride and sodium (and potassium) is not necessarily present, especially after doses in the physiological range. The effects of the hormone on electrolyte excretion probably depend upon a number of factors such as the electrolyte stores of the body, the electrolyte in the diet, the rate of secretion of adrenal cortical steroids, etc.

What is the nature of the antidiuretic hormone? It is a stored product which some believe is secreted by the supraoptic neurons from which it has been transported to the posterior lobe by way of the connecting axons of the stalk. In respect of the storage of its hormones, the neurohypophysis has more resemblance to the thyroid and adrenal medulla than to the adrenal cortex in which there is very little storage of hormones. The adult human posterior pituitary contains about 15,000 milli-units (m.u.) of antidiuretic hormone.[8] The amount required by a man for the normal control of the renal excretion of water appears to range between 7.5 and less than 50 m.u. per hour.[9] The amount which can be detected is exceedingly small: for example, by intravenous injection, a detectable effect on the urinary excretion of water in man can be obtained by 0.5 to 2 m.u.[10] The most potent preparation of

antidiuretic principle is that which Turner, Pierce and du Vigneaud extracted.[11] This polypeptide containing only 8 amino acids had a potency of at least 600,000 m.u. per milligram in some preparations. The great potency of this preparation can be appreciated from the fact that a dose which will produce a definite antidiuresis in man is only 1/300,000th of a milligram or less.

The control of the release of antidiuretic hormone is complex. The important supraoptic nuclei and the less important paraventricular nuclei have many possible connections with cortical and subcortical levels for the facilitation or inhibition of liberation of the hormone. Examples of the nervous control of the release of hormone are furnished by a number of observations. Claude Bernard was perhaps the first to note that emotion may interfere with diuresis. Later experiments, especially those of Verney and his colleagues, have demonstrated that noise or painful stimuli can cause the liberation of antidiuretic hormone from the neurohypophysis.[12, 13] These experiments were performed in dogs; it appears probable that many other mammals including man likewise have a very labile nervous mechanism for the release of antidiuretic hormone.[14] Another example is furnished by the experiments of Ames and van Dyke[15] in the rat in which a painful stimulus such as heart puncture is accompanied by the release of considerable amounts of antidiuretic hormone into the blood. Ether anesthesia produced a similar effect. Some of their results are illustrated in Figure 3.

Many experiments have been performed to demonstrate the importance of water in regulating the release of antidiuretic hormone. Probably water diuresis can be considered a form of mild diabetes insipidus since the effect of water is to reduce the rate of release of the hormone. On the other hand if an inadequate amount of water is available to the organism the hormone is then liberated at an increased rate. Gilman and Goodman were able to detect the hormone in the urine of dehydrated rats.[16] Verney[17] carried out many experiments in dogs to establish the importance of water in regulating the liberation of hormone; for example, an increase of only 2 per cent in the osmotic pressure of the carotid blood on one side is sufficient to cause a measurable increase in the rate of liberation of antidiuretic hormone. Verney suggests that specific receptors, identified morphologically as vesicles in the hypothalamus, act as osmometers and thus initiate the liberation of antidiuretic hormone when the osmotic pressure of the plasma rises. Re-

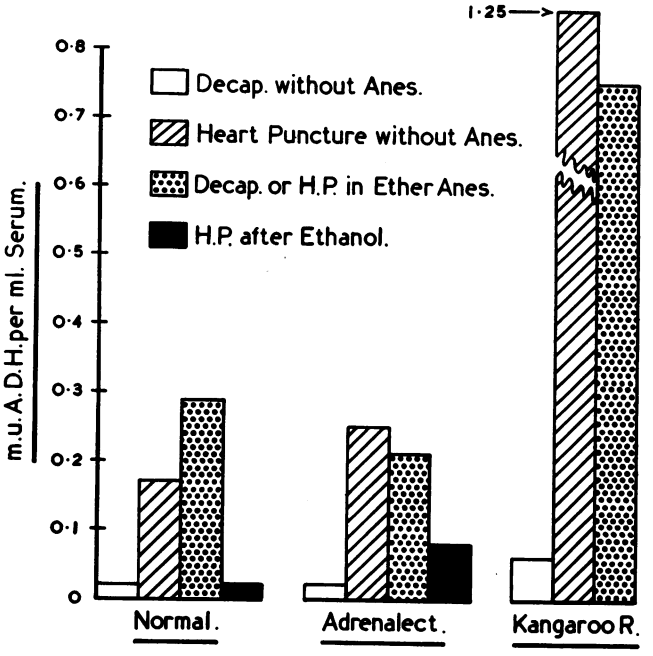

Fig. 3—Levels of antidiuretic hormone in the blood of Long-Evans laboratory rats (normal and adrenalectomized) and in kangaroo rats (*Dipodomys merriami*).

The levels are low or very low if blood was obtained by sudden decapitation without excitement. After heart puncture or ether anesthesia (pain or excitement), high levels were found. Ethyl alcohol inhibited the release of hormone.

The kangaroo rat is a desert rodent which normally has no access to water and excretes very concentrated urine. Its neurohypophysis can release comparatively large amounts of hormone. (From data of Ames and van Dyke.[15])

cently, stress has been placed on the importance of the volume of the extracellular fluid as another factor influencing the rate of liberation of the antidiuretic hormone.[18] Expansion of the volume of plasma or total extracellular fluid is believed to lead to a decreased liberation of the hormone whereas contraction is considered to have the opposite effect.

Hormones and drugs also either increase or diminish the rate of liberation of the antidiuretic hormone. Acetylcholine causes an increased liberation of the hormone and this effect can be demonstrated by the injection of minute amounts of this base near the supraoptic neurons. Epinephrine can transiently interfere with the hormone's liberation; larger amounts cause an increase in the rate of liberation.

The exact mechanism by which epinephrine and its related amine, norepinephrine, facilitate a liberation of the hormone is still under discussion. Many drugs cause antidiuresis in normal animals but produce this effect either not at all or much less strikingly in animals with diabetes insipidus. These facts strongly suggest that they cause the liberation of antidiuretic hormone in normal animals. To this group of drugs belong ether, phenobarbital, morphine, dimercaprol, yohimbine, nicotine and 3-hydroxy-2-phenyl cinchoninic acid and related compounds. The hepatic vasodepressor substance (VDM), identified as ferritin, likewise causes the release of antidiuretic hormone.[19] An example of a drug which has the opposite effect, an interference with the release of the hormone, is ethyl alcohol.

We shall later see that knowledge of all these facts has been applied in detecting diabetes insipidus; for example, the presence of a functioning neurohypophysis may be established by the excretion of hypertonic urine after dehydration or by the appearance of antidiuresis after the administration of a drug like nicotine.

Clinical Considerations

Deficiency of antidiuretic hormone: If the amount of hormone secreted is inadequate, varying degrees of polyuria characterized by large amounts of urine of low specific gravity appear. In true diabetes insipidus the polyuria is primary; the associated polydipsia serves to keep the organism in water balance. The differential diagnosis of diabetes insipidus from disorders such as hysterical polydipsia has usually been accomplished either by raising the osmotic pressure of the body fluids or by the injection of drugs. For the first method Hickey and Hare[20] advocated the intravenous injection of 2.5 per cent sodium chloride to ascertain whether or not an inhibition of water diuresis would occur in the subject. Other clinicians prefer a simple prolonged dehydration to determine whether there is an associated liberation of antidiuretic hormone as demonstrated by an acceptable increase in the specific gravity of the urine (e.g., 1.024 or higher). Nicotine intravenously has also been used to detect neurohypophysial secretion. Cates and Garrod[21] as well as Lewis and Chalmers[22] could show that moderate doses of nicotine cause no antidiuresis in the majority of patients with true diabetes insipidus whereas the alkaloid has such an effect in normal subjects (See Figure 4). As is well known, the therapy

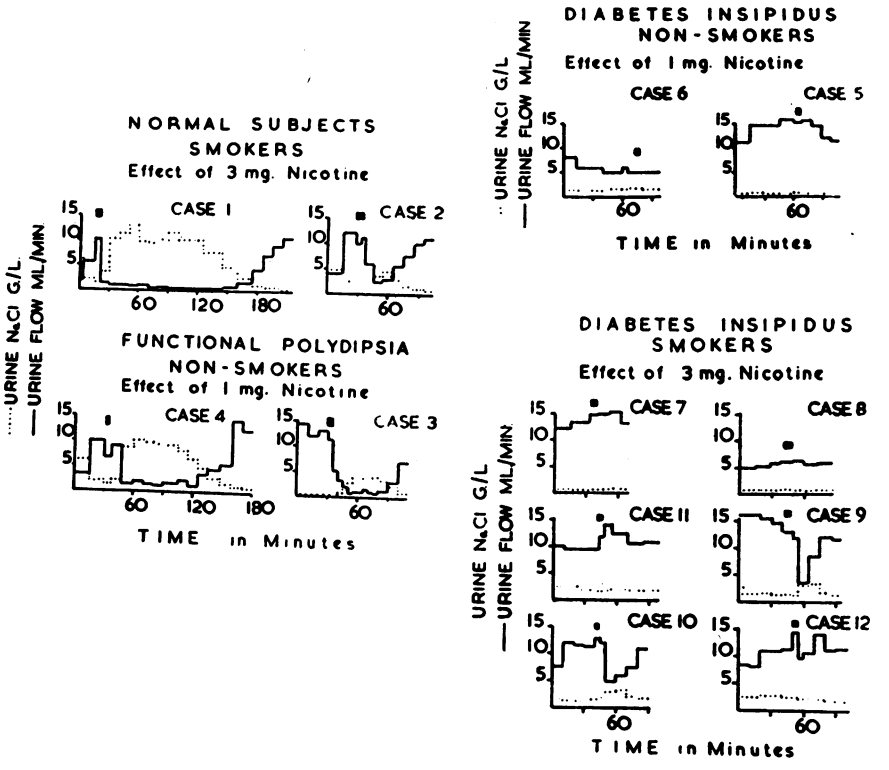

Fig. 4—The effects of intravenous nicotine in smokers and non-smokers with and without diabetes insipidus (from Cates and Garrod[21] in *Clinical Science 10*:145-60, 1951. Reprinted by permission). Note the antidiuretic effect of nicotine in normal subjects and its absence in the majority of the patients (except cases 9 and 10) with diabetes insipidus. In later experiments antidiuresis after *large* doses of nicotine could be demonstrated in all the cases except case 6 and possibly case 12.

of diabetes insipidus requires the administration of posterior-pituitary extract rich in antidiuretic principle.

Hypersecretion of antidiuretic hormone: Hypersecretion of antidiuretic hormone for prolonged periods because of disease has not been convincingly demonstrated. The evidence favoring the view that hypersecretion occurs in cirrhosis with ascites, in adrenal insufficiency, in toxemias of pregnancy as well as in a number of other diseases is based upon the presumed recognition of excessive amounts of antidiuretic hormone in the urine or blood of patients. Usually the assays have been performed by subcutaneous or intraperitoneal injection in hydrated normal rats. This is not a specific test for antidiuretic hormone. A much

more satisfactory test which can be adequately controlled is the production of transient antidiuresis after the intravenous injection of the test material in hydrated normal dogs or dogs with diabetes insipidus. In one study in which this method of assay was used to examine the urine of patients with cirrhosis of the liver, the urinary titer of antidiuretic hormone was only slightly higher in the ascitic patients compared with those clinically free from ascites.[23]

SUMMARY

The neurohypophysis, consisting of the supraoptic and paraventricular nuclei, their axons and the posterior lobe of the pituitary in which these axons terminate, is an endocrine unit of great importance for the regulation of the excretion of water. The antidiuretic hormone, a secretion of this unit, is almost entirely stored in the posterior lobe. It favors water conservation by causing an increased reabsorption of water by the kidneys. A deficiency of the hormone's secretion causes a pronounced renal loss of water as in diabetes insipidus; compensation is achieved by polydipsia.

Transient liberation of antidiuretic hormone can be provoked by pain or excitement, dehydration, large doses of electrolyte (NaCl) and by drugs. Although it has been asserted that prolonged hypersecretion of the hormone probably occurs in certain diseases, acceptable evidence in favor of this hypothesis has not been furnished.

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