THE HYPOTHALAMO HYPOPHYSEAL SYSTEM

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The hypothalamo hypophyseal neurosecretory system is concerned with the production and secretion into the blood stream of the two hormones—oxytocin and vasopressin: the former is an uterine muscle contractant and lactogenic principle, the latter having important antidiuretic effects.

FUNCTION OF THE HORMONES

The effects of these two hormones show a considerable amount of overlap: both seem to exert the following functions:

a)	uterine muscle contraction	Principally oxytocin
b)	milk ejection	
c)	anti diuresis	Principally vasopressin
d)	vasoconstriction	

Vasoconstriction is only brought about when vasopressin is administered in pharmacological doses: in the body it is not secreted in sufficiently large amounts to cause vasoconstriction. Thus the name vasopressin usually ascribed to it is a misnomer. The principle effect of this hormone under physiological condition is antidiuresis (water conservation), so that a better name for it is Antidiuretic Hormone (ADH), and it is as ADH that we shall consider it in this article.

SYNTHESIS OF THE HORMONES

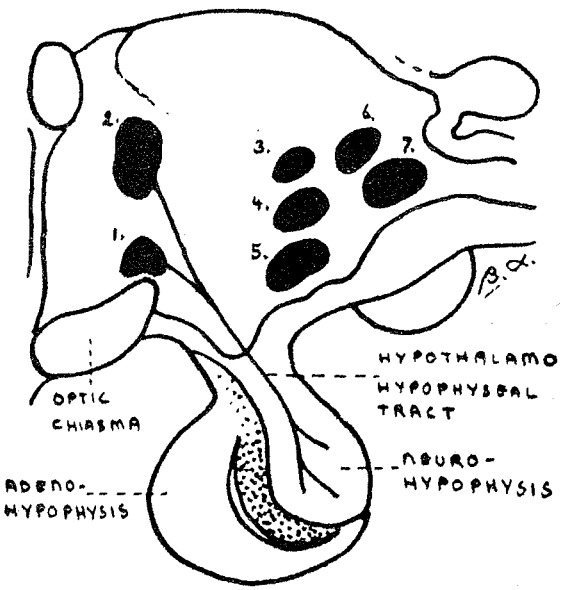
Sharrer and Sharrer attributed the synthesis of these two hormones to the supraoptic and paraventricular nuclei of the hypothalamus(1). They observed that the soma of the neurones in these nuclei apart from having all the characteristics of nerve cells, have also the characteristics of glandular cells being vacuolated and granular. These granules were shown by Bargmann to stain with Chrome Alum Haematoxylin (Gomori's stain) abbreviated to CAH i.e. they are CAH-positive (2).

There exists a definite axonal tract (the hypothalamo hypophysal tract) between the supraoptic and paraventricular nuclei of the hypothalamus and the neurohypophyses, and this CAH-positive material has been shown to move down the tract to the neurohypophyses(3).

NEUROSECRETION

The foregoing considerations raise the possibility of neurosecretion, and this has been the subject of a number of interesting experiments.

DIAGRAMATIC SAGITTAL SECTION THROUGH THIRD VENTRICLE TO ILLUSTRATE POSITIONS OF NUCLEI.



1. SUPRA-OPTIC NUCLEUS
2. PARAVENTRICULAR NUCLEUS
3. DORSIMEDIAL NUCLEUS
4. TUBER NUCLEUS
5. VENTRIMEDIAL NUCLEUS
6. LATERAL NUCLEUS
7. POSTERIOR NUCLEUS

1. Hild and his co-workers(4) cut through the hypothalamo hypophyseal tract and found, that whilst the part of the tract above the lesion showed an accumulation of the CAH-positive material, the part below it was devoid of such material.

2. Hild(5) obtained extracts of ADH and oxytocin from various sites of accumulation of CAH-positive material i.e. from the soma, axons and neurohypophysis itself.

3. Leveque and Sharrer(6) found that the amount of CAH-positive material down the tract bore a definite relation to the osmotic state of the plasma, i.e. it was abundant when the body was in a state of dehydration, and virtually absent in the presence of a water load.

4. Arnott and Sloper injected 35-S Cysteine into the cisternal space of an animal and subjected the dead animal to autoradiography. They found that the radio active material was rapidly taken up by the supraoptic and paraven-

tricular nuclei, and only after some time did it appear in the neurohypophysis. This cannot be due to a lack of blood supply of the neurohypophysis as this is well outside the blood brain barrier. Hence the cysteine must be actively used up by the supraoptic and paraventricular nuclei; in fact, cysteine is incorporated into the hormonal percursor, and is then converted to cystine.

From the above experimental data, one can readily appreciate the intimate relationship of the CAH-positive material with the octapeptide hormones, the former was demonstrated however, to be chemically distinct from the latter by various workers(7). The CAH-positive material is thought to be the carrier of the hormone precursor(8), which is synthesized in the soma of the neurones of the supraoptic and paraventricular nuclei, and which is carried down via the hypothalamo-hypophyseal tract to the neurohypophysis.

The endings of the tract are in intimate relationship with both the pituicytes (modified astroglia, abundant in the neurohypophysis) and the blood vessels of the neurohypophysis(9). It is thought that the hormone precursor passes to the pituicytes, which break it down into its active octapeptide form, and send it into the blood stream when the need arises(10). The neurohypophysis is an excellent storage depot for the hormone, as it is well outside the blood brain barrier(11), and has a very rich blood supply(12), as well as very permeable capillaries, so that the active hormone(s) may swiftly be ejected into the blood when required.

Evidence is now accumulating, suggesting that the hormone precursor is not only synthesized in the soma of the supraoptic and paraventricular nuclei, but also in their axons i.e. apart from axoplasmic streaming, there is a progressive synthesis of the hormone precursor(13).

CONTROL OF THE SECRETION OF ADH AND OXYTOCIN

It was shown by Verney in his "Carotid Loop" experiment, that the osmotic pressure of the plasma solutes is the factor which controls the secretion of the posterior pituitary hormones. The osmotic pressure acts on what Verney called osmoreceptors, and these then relay the stimulus to the neurohypophysis.

By means of intradural ligation, Verney and Jewell, in 1953, demonstrated that the osmoreceptors are situated in some part of the prosencephalon(14). Verney noticed small vesicles situated in the supraoptic nucleus of the dog and ascribed to them the function of osmoreceptors(15). This assumption seems improbable.

The exact site of these osmoreceptors is as yet not known, though some very interesting work in this direction was carried out by Sawer. Abraham and Pickford (1954) showed that upon injection of hypertonic saline, the posterior pituitary secreted oxytocin and ADH in the ratio of 30:1. Thus, there occurred a rise in intramammary pressure. Why there should be a rise in intramammary pressure as a result of an osmotic stress, is a mystery. Now Sawer(16) cannulated the mammary duct of a rabbit, and inserted bipolar electrodes deeply into the ventral telencephalon between the olfactory tubercle and the lateral preoptic area. He noticed, upon administration of an osmotic stress, an increased rate of firing in the neurones here, immediately before any rise in intramammary pressure: transection of the midbrain did not affect the firing or milk ejection response. Thus he concluded, that the osmoreceptors are situated here. This evidence however, is not conclusive.

An interesting point is, that oxytocin is also secreted in the male, but its function is not known: a similar state of affairs in the male exists with the anterior pituitary hormone prolactin.

Olivecrona found that bilateral destruction of the paraventricular nuclei in the rat results in a loss of extractable oxytocic material from the neurohypophysis. A neurohypophysis completely lacking oxytocin shows a normal pressor content(17). Again, an application of an osmotic stress was seen to accelerate the rate of firing of the supraoptic units and inhibit those of the paraventricular units(18); the direct stimulation of the paraventricular nucleus carried out by Cross(19), resulted in a marked milk ejection response.

This evidence would suggest that the supraoptic nucleus is concerned with ADH production, while the paraventricular nucleus is concerned with oxytocin production. There cannot be any clear cut line of demarcation however. Thus, although in the face of osmotic stress, there occurs an increase in the spike frequency in the cells of the supraoptic nuclei, relative to the paraventricular nucleus, more oxytocin than ADH is in fact secreted (see above).

Many factors other than the osmotic pressure of the plasma solutes, stimulate the secretion of the posterior pituitary hormones: a decrease in the extracellular volume as occurs in haemorrhage, for example, will stimulate secretion of the hormones (acting on stretch receptors in the great vessels). But the principal stimulus for secretion of these two hormones, is the osmotic pressure of the plasma solutes.

It may be pointed out as a matter of historical interest, that various workers, principally Abel, postulated that oxytocin and ADH are in

fact a single hormone exhibiting both oxytocic and antidiuretic activities (the "Unitarian Theory)(20). The existance of two individual hormones was proved by a number of different workers, but principally by du Vigneaud(21).

SUMMARY

The probable sequence of events leading to the release of the two octapeptide hormones in the face of an osmotic stress may now be summarized into four basic stages.

1. The osmotic pressure of the plasma solutes acting via the blood in the internal carotid artery stimulates the osmoreceptors in the ventral telencephalon.

2. The osmoreceptors stimulate the supraoptic and paraventricular nuclei: these two nuclei are probably producing the hormone precursor all the time, storing it in the pituicytes.

3. The stimulus is relayed down the hypothalamo hypophyseal tract to the pituicytes.

4. The pituicytes then release the active octapeptide into the blood stream.

Upon reaching the kidney ADH increases the permeability of the distal convulted tubules and collecting duct, so that water may pass out of the nephron and enter the interstitium, from where it is conducted away by the blood vessels. Hence water economy is achieved.

INTERRELATION OF THE ANTERIOR AND POSTERIOR PITUITARY

The antidiuretic action of ADH is abolished by severence of the pituitary stalk, but an increased excretion of water occurs only as long as there is an intact ANTERIOR pituary. In man, lesions leading to the destruction and degeneration of the neurohypophysis, can result in Diabetes Insipidus ,provided that there is an intact anterior pituary. Diabetes Insipidus is characterized by a polyuria of up to 20 litres per day, the urine excreted being very dilute and having a very low specific gravity: this polyuria is coupled naturally with a severe polydypsia.

There exists a relationship between ADH, the anterior pituitary and the corticosteroids relative to diuresis, but it is not well understood(22). It has been shown that fibres from the supraoptic and paraventricular nuclei of the hypothalamus containing CAH positive material, pass to the pars tuberalis and possibly also to the pars distalis of the anterior pituitary. These fibres come into contact with the radicles of the hypophyseal portal vessels in the median eminence and infundibular stem. The corticosteroids appear to have a direct effect on the action of the neurohypophysis, and it is possible that they are involved in the activation of the neurohypophyseal hormones. There also appears to be some connection between ADH and ACTH formation(23).

CONCLUSION

The mechanism of the hypothalamo-hypophyseal system is far from clear; there is a great deal of overlap with other humoral and neural mechanisms. At the moment the neurosecretory origin of the posterior lobe hormones remains the most attractive hypothesis. It offers a clear and reasonable explanation for the lack of secretory elements in the neurohypophysis and for the antidiuretic-pressor substance in the hypothalamus as well as for the very existence of the hypothalamo-hypophyseal tract itself.

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