

RECENT ADVANCES IN NEUROENDOCRINOLOGY

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The integration of the functions of the various organs in the body during rest and activity and under conditions of changes in the external and internal environment is accomplished through the functions of the nervous system and endocrines. These mechanisms are likewise at work under pathological conditions. Thus tissue damage results in adjustment reactions consisting of nervous discharges and quantitatively altered internal secretion. Even the gross anatomical changes in various organs, particularly the adrenal cortex and the lymphatic tissues as seen in Selye's alarm reaction are the result of neuro-endocrine activity. For a better understanding of the behaviour of the organism a knowledge of the mutual relationships of these two integrating systems is of paramount importance.

It is almost an axiom in endocrinology that the surgical removal of a gland of internal secretion followed by its implantation in some other part of the body is not accompanied by any endocrine disturbance provided that the implant remains viable. This has been exemplified in the cases of removal and subsequent implantation of gonads, thyroid, adrenal cortex, pancreas and anterior pituitary. From these findings it follows that the implanted endocrine organ retains its ability to produce an internal secretion. Factors such as blood sugar level continue to influence insulin secretion in the denervated pancreas, and likewise the level of various hormones in the blood and tissues remains an effective regulator of the rate of internal secretion from implanted organs. These observations might suggest that nervous system is only of minor, significance, if any for the activity of the endocrine system. However, such a sweeping generalisation would be quite erroneous, since detailed investigations show that the role of the nervous system varies considerably for different glands of internal secretion.

A. NERVOUS INFLUENCE ON ENDOCRINE ACTIVITY

Figure 1 gives a schematic representation of the connections of the neurohypophysis system. This will indicate the close interrelationship that exists with anterior pituitary gland.

(1) **Anterior Pituitary:**

(a) *The Nervous control of the Gonadotrophic Hormones*—That certain activities of the gonads are dependent on the nervous system is common clinical experience.

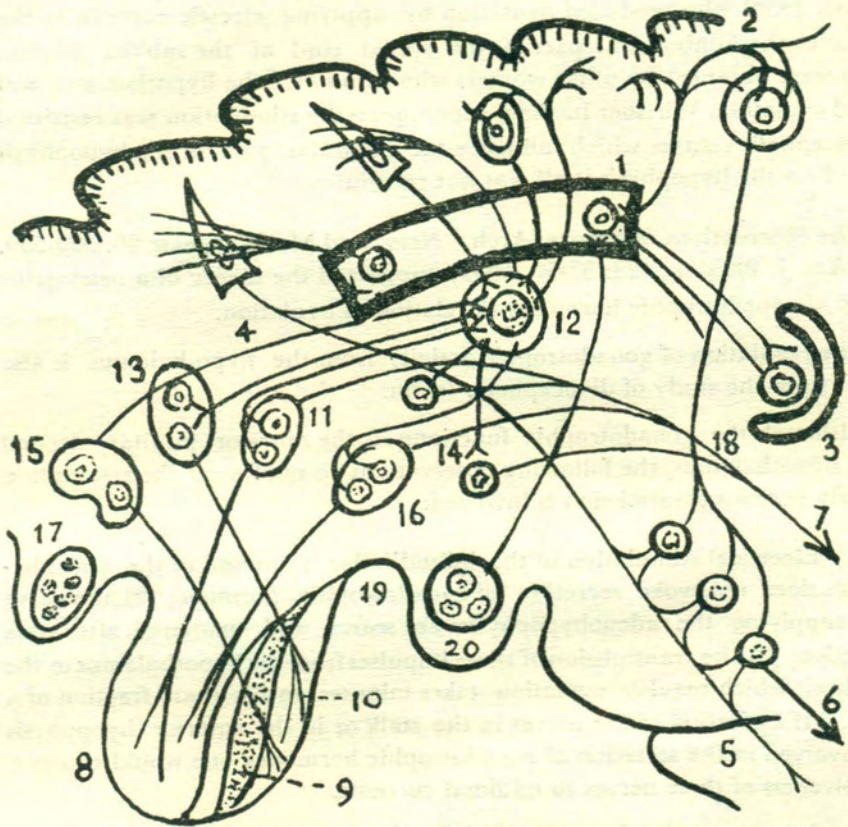


Fig. 1—Connections of the neurohypophysis system. (1) Inner cerebrum. (2) Pre-frontal cerebral cortex. (3) Temporal cortex. (4) Frontopontine tract. (5) Fasciculus longitudinalis dorsalis. (6) Mesencephalic reticular tract. (7) Schultze's tract. (8) Hypophysis, anterior lobe. (9) Hypophysis, medial lobe (pars intermedia). (10) Hypophysis, posterior lobe. (11) Nucleus hypothalamicus dorsomedialis. (12) Nucleus dorsomedialis of the thalamus opticus. (13) Nucleus paraventricularis. (14) Nuclei tuberes. (15) Nucleus supra-opticus. (16) Nucleus hypothalamicus ventromedialis. (17) Optic chiasma. (18) Mesencephalic reticular system. (19) Pituitary stem. (20) Corpora mammillaria.

The experimental work in which the hypothalamic-hypophysial relationship of the gonadotrophic hormones was established may be divided into several groups. In the first the effect of stimulation of the hypothalamus and of the nerves supplying the anterior hypophysis was studied. In the rabbits

ovulation (which does not occur spontaneously but follows sexual intercourse) served as an indicator of the release of gonadotrophic hormones from the hypophysis.

The pioneer work was done by Marshall and Verney (J. Physiol. 86: 327-336, 1936) who produced ovulation by applying electric currents to the head or to the lumbosacral part of the spinal cord of the rabbit. Similar results were obtained by other workers who stimulated the hypothalamus and elicited ovulation. Whether in these experiments the stimulation was restricted to diencephalic centres which influence the glandular part of the hypophysis or acted on the hypophysis itself was not certain.

The observations of Brooks (Arch. Nerv. and Ment. Disease 20: 525-550, 1940; Am. J. Physiol., 128: 57-60, 1939) supported the theory of a neurogenic control of gonadotrophic hormones in relation to ovulation.

The regulation of gonadotrophic activity from the hypothalamus is also evident from the study of diencephalic lesion.

Although the gonadotrophic functions of the anterior pituitary depend on the hypothalamus, the following observations do not favour the assumption that only nervous transmission is involved:

(1) Electrical stimulation of the infundibular stem and of the adenohypophysis does not evoke secretion of gonadotrophic hormone; (2) the nerve fibres supplying the adenohypophysis are scarce and unaltered after stalk transection; (3) the transmission of those impulses from the hypothalamus to the hypophysis which regulate ovulation takes minutes rather than fraction of a second. If excitation of the nerves in the stalk or in the anterior hypophysis were involved in the secretion of gonadotrophic hormones one would expect a responsiveness of these nerves to minimal currents.

An alternate mechanism suggested by Harris is that of a neurohumoral transmission. According to him the hypophysial portal system seems to carry the neurohumors released by hypothalamic excitation of anterior pituitary. This view has been challenged by Zuckerman who was able to induce estrus in ferrets artificially after severance of vascular connections between the hypothalamus (medium eminence) and the anterior pituitary.

In this connection indications are there that spontaneous ovulation and cyclicity of estrus in the rat are controlled by hypothalamic mechanisms. It would be of interest to examine whether the same type of neuronal mechanisms operate in other spontaneously ovulating forms, such as primates. In these days of pre-occupation with search for anti-ovulatory compounds for use as anti-fertility agents such basic informations are of considerable importance.

Harris believes that even puberty, anestrus and menopause are influenced by stimuli originating from hypothalamus and affecting hypophysial activity.

(b) *The neural control of the Secretion of the Thyrotrophic Hormone*—Numerous attempts have been made to demonstrate the action of autonomic nerves on the secretion of thyroxine and thyroglobulin, but the results have largely been negative. Stimulation of the cervical sympathetic trunk furnished no evidence for the presence of secretory nerves of the thyroid gland since thyroid hormones in the blood were not increased. The attempts of Cannon et al. (Am. J. Physiol., 36:, 363-364, 1914; Endocrinology, 26: 142-152, 1940) to enhance the sympathetic discharges to the thyroid gland, by anastomosing the phrenic nerve with the peripheral fibres innervating the thyroid gland, produced signs of heightened thyroid activity only in a small percentage of cases and negative results in the hand of others investigators. Experiments with prolonged stimulation of the cervical sympathetic also have led to conflicting results. The fact that the whole sympathetic chain can be removed without significantly altering the metabolic rate suggests that the sympathetic fibres supplying the thyroid do not modify the secretion of the thyroid hormones under physiological conditions. Apparently the sympathetic nerves do not carry secretory fibres to the thyroid gland. Moreover the experiments seem to indicate that the secretion of the thyroid hormones is largely independent of wide variations of the autonomically controlled blood supply. However, it should not be inferred that the nervous system is without influence on the thyroid gland.

(c) *The Nervous Control of ACTH*—The recent views regarding the neural control of ACTH secretion state that under *optimum resting conditions* the main stimulus to release of this hormone is some hypothalamic "drive" operative *via* the hypophysial portal vessels. The peripheral blood level of corticoids probably helps to maintain a more constant pituitary secretion of ACTH. *Under stressful situations*, however, either one or both of these mechanisms may be brought into play. Firstly, what may be called neural stress stimuli appear to stimulate ACTH release by means of nervous reflex pathways acting through hypothalamus and hypophysial portal vessels. And secondly systemic stresses that cause tissue damage or metabolic changes, probably excite ACTH secretion both by neural reflex activation of the hypothalamus and by producing changes in the chemistry of the systemic blood which in turn affects pituitary tissue directly. It is probable that sympathicomedullary system may play a subsidiary role in stimulating ACTH release. Additionally, it has been suggested that the pituitary stalk forms a connecting link between the external environment and central nervous system on the one hand and the pituitary-adrenal axis on the other. The adrenocortical atrophy that follows pituitary

stalk section has been explained on the basis of removal of "tonic" environmental stimuli which normally operate to maintain ACTH secretion.

(d) *The Nervous control of Somatotrophin (Growth Hormone)*—Few studies seem to have been made of any control exerted by the hypothalamus over the secretion of growth hormone. However, it has been reported recently that increased insulin sensitivity of hypophysectomized rats, or of rats in which electrolytic lesions have been placed in the hypothalamus, may be reduced to normal by administration of somatotrophin.

2 Posterior Pituitary :

(i) *The Neural Factor in the Secretion of Antidiuretic Hormone*—The role of nervous impulses in the secretion of hormones is perhaps still greater for the posterior pituitary than it is for the adrenal medulla. The fundamental principles were established through the classical experiments of Fisher, Ingram and Ranson, who determined the influence of discrete hypothalamic lesions on the secretion of the antidiuretic hormone of the posterior lobe. They found in cats and monkeys that diabetes insipidus results regularly from lesions which interrupt the supraoptico-hypophyseal tract. Such lesions lead to a degeneration of supraoptic nuclei and are followed by atrophy of the posterior lobe. The severity of this syndrome is directly related to the number of nerve fibres which have degenerated. If, however, the lesion involves the tubero-hypophysial tract no changes in the posterior lobe function occur and the urinary secretion remains normal.

The theory of Ranson and his collaborators has steadily gained ground and appears to be applicable to the human beings.

(ii) *The Nervous Regulation of the Pressor Hormones of the Neurohypophysis*—Since the pressure and antidiuretic principles of the posterior pituitary seem to represent two different effects of the same substance, one would expect that direct or reflex activation of the neurohypophysis would liberate this vasopressor hormone.

Several workers have shown that a pressor response may be elicited through afferent vagal impulses in animals in which the nervous connections between the brain and the spinal cord are completely severed while the vascular connections between the head and trunk remain intact. This effect on blood pressure is abolished after transaction of the stalk. The results indicate that vagal impulses lead to a release of the pituitary hormones which bring about a rise in blood pressure.

(iii) *The Nervous Control of Oxytocic Hormone*—Recent studies present conclusive evidence for a physiological role of the neurohypophysis in uterine

contraction during labour. This evidence rests on the disturbances in parturition in animals with destruction of the supraoptico-hypophysial system, the liberation of the oxytocic principle on hypothalamic stimulation and the similarity of the latter effect to the effect of posterior pituitary extract when injected intravenously.

There is another function of oxytocin and it depends likewise on the hypothalamus for its liberation: the ejection of milk from the lactating mammary gland. The secretion of milk is regulated by the lactogenic hormone of the anterior pituitary, but its ejection in the lactating animals is influenced by the oxytocic fraction of the posterior pituitary. Stimulation of the anterior hypothalamus particularly of the supraoptic nuclei and their intermediate vicinity induces ejection of milk in lactating animals.

(3) **The Nervous Control of the Adrenal Medulla :**

Figure 2 gives a diagrammatic representation of the neuroendocrine and neurovegetative metabolic integration which is now known to exist. The importance neuro-endocrine relation is further clearly seen in the adrenal medulla; the chief function of the adrenal medulla, the adjustment of the rate of adrenaline secretion to conditions of emergency (Cannon) depends on the integrity of the splanchnic nerves.

The secretion of adrenaline is regulated by autonomic centres in the hypothalamus and medulla oblongata; the spinal centres play only a subordinate role. Reflex excitation via the carotid sinus pressoreceptors is thought to be responsible for the variations in the rate of adrenaline secretion, when the blood pressure is experimentally varied. Changes in the chemical composition of blood, particularly with respect to oxygen and glucose are known to activate the sympathetico-adrenal system and to increase the concentration of circulating adrenaline. Anoxia and asphyxia as well as hypoglycaemia are particularly potent activators of adrenomedullary secretion.

It may be concluded that a great variety of conditions lead to the activation of the adrenal medulla through discharges originating in the centres of sympathetic system. These discharges are initiated reflexly/or directly. Stimuli such as lowered temperature of the blood and the complex processes associated with emotion may serve as examples for direct action on the hypothalamus. In other conditions such as barbiturate anaesthesia and hypoglycaemia, cortical control, seems to be the decisive factor in effecting a discharge of adrenaline.

The physiological role which adrenaline plays in the organism depends on the integrity of the splanchnic nerves.

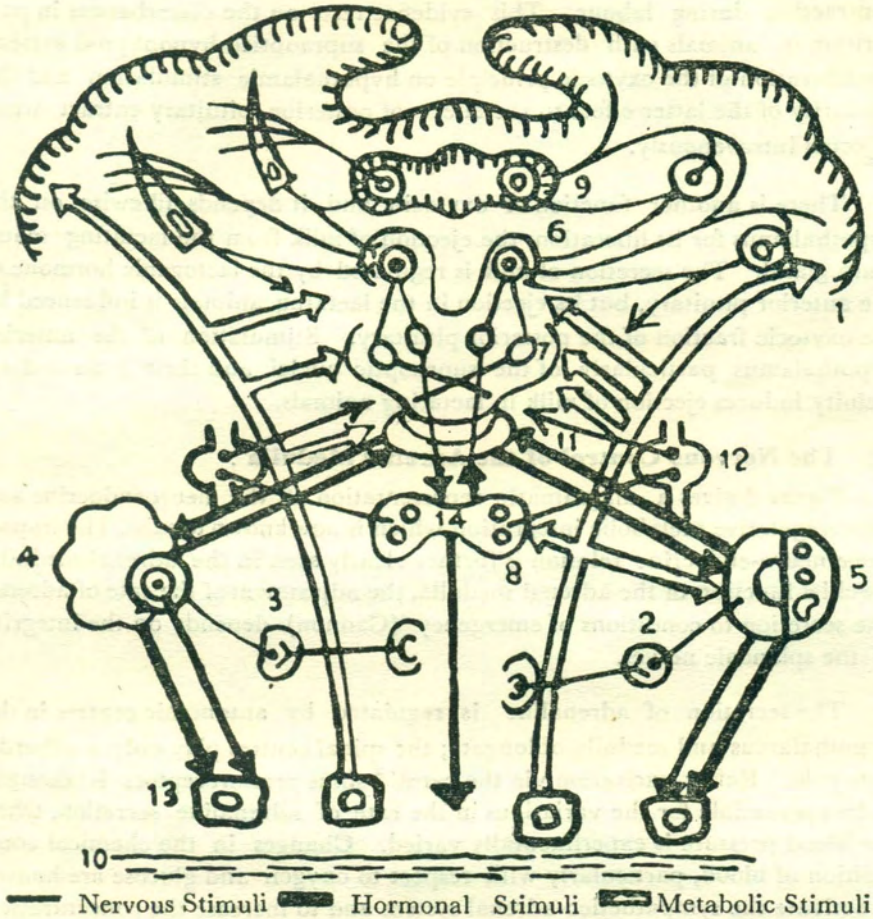


Fig. 2—Neuroendocrine and neurovegetative metabolic integration. (1) Cerebral cortex. (2) Mesenteric ganglion. (3) Semilunar ganglion. (4) Adrenal glands. (5) Sexual glands. (6) Nuclius dorsomedialis of the thalamus opticus. (7) Mediolateral (8) Parathyroid glands. (9) Rhinencephalon. (10) Macromolecular system. (11) Neurohypophysis system. (12) Sympathetic nervous system. (13) Tissular system. (14) Thyroid glands.

(4) The Neural Control of Pancreas:

Since the implanted pancreas secretes insulin in adequate amounts and prevents the occurrence of diabetes mellitus in pancreatectomised animals, the influence of nerves supplying the pancreas can consist only in modifying the rate of insulin secretion. The fact that fibres of the right vagus innervate the islets of Langerhans furnishes the anatomical basis for the possible significance of the vagus in the regulation of insulin secretion. The important observation that stimulation of the right vagus causes hypoglycaemia which is absent

when the pancreatic vein is ligated suggests that the secretion of insulin is regulated under physiological conditions, at least in part, by nervous impulses. Some evidence is available to indicate that the sugar content of the central nervous system may determine the degree of vagal insulin secretion.

In the light of the effects on the vago-insulin system obtained by stimulation of the hypothalamus and in emotional excitation, it may be suggested that insulin secretion is regulated, at least in part, at the hypothalamic level. The mechanism by which hyperglycaemia influences the parasympathetic system in diencephalon and the particular parts involved are not known. The decrease in cortical function with the attending release of the brain stem in anoxia may play a role in activating not only the sympathetico-adrenal but also the vago-insulin system.

B. RECIPROCAL INFLUENCE OF ENDOCRINES ON NERVOUS ACTIVITY

The relation of thyroid hormone to the cortical activity is well known. The administration of thyroxin increases the alpha frequency of the EEG in man. The action of thyroid hormone is generally interpreted as being due to rise in brain metabolism. Although data on this point are controversial, the observation that sensitivity of the brain to anoxia is increased in hyperthyroidism supports this argument. The intensification of conditioned reflexes through thyroid feeding, the increased sensitivity of the light reflex, and the augmented response of the centres of sympathetico-adrenal system in hyperthyroid animals show that the excitability of all parts of the central nervous system is raised by thyroid hormone. The converse is also true, as observations on nervous functions in thyroidectomised animals indicate.

The relation of adrenocortical hormones to brain functions has also been investigated. The EEG of adrenalectomised rats shows a shift towards lower frequency. The normal range can be restored by adrenocortical extracts and α_5 -pregnenolone but not by desoxycortico-sterone (DCA). Whether the slowing which occurs in Addison's disease is the result of metabolism is not clear. The relation of adrenocortical hormone to the excitability of the brain has been elucidated through electrically induced convulsion. The convulsive threshold is lowered after adrenalectomy and restored to normal by DCA or sodium chloride. When administered to the normal animal DCA raises the convulsive threshold, and this effect can be counteracted by cortisone or ACTH. These effects are apparently related to changes in the concentration of plasma sodium and consequently to those adrenocortical hormones which like DCA affect the sodium balance of the organism.

In this lecture, I have tried to summarise in broad outline the basic concepts relating to the interrelationships and integration of the neuro-endocrine system. It is this functional unity of the neuro-endocrines which is primarily responsible for maintenance of homeostasis and which makes the organism a single vital entity capable of biological adaptation and survival.