NEUROLOGICAL ENDOCRINOLOGY: THE COORDINATING MECHANISM

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The nervous and endocrine systems are integrative in nature for they provide the organism with sophisticated external and internal sensing devices which feed information into the central nervous system for appropriate responses of the target systems

THE production and dispersal of chemical substances within an organism which subserve definite integrating and coordinating roles, and thereby supplement the activity of the nervous elements, are characteristic of all living things. Such substances may be referred to as chemical coordinators. In short, every substance which enters body fluids from the external environment or from constituent cells of a higher organism contributes to the normal composition of the internal medium is a chemical coordinator. Such chemical coordinators may be more restricted in their region of origin within the body and adaptively participate in a specialised activity within the organism. Many groups of higher organisms have specialised glandular cells, tissues or organs which produce such coordinatory substances for the organism as a whole.

The most important point to emphasize for comparative physiological purposes is that in a number of phyla and classes of animals special chemical substances are produced which are essential to normal development and functional integration of the body. The points of origin within the organism, the specific chemical nature of the hormones and the methods of transport are secondary in importance. The nature of the resultant effects depends as much on the nature of the reacting tissues as on the chemical properties of the circulating hormone. The ability to maintain constancy is observed to a high degree of development in the mammals through the integration of nervous and hormonal systems and to a lesser extent in the lower vertebrates. The invertebrates also have similar mechanism of regulation, although they are considerably less exacting. The two major integrative systems of the body, the nervous and endocrine systems, are intimately interrelated functionally. The nervous and endocrine systems are integrative in nature, for they provide the organism with sophisticated external and internal sensing devices which feed information into the central nervous system for analysis and integration, and in turn orchestrate the necessary target systems to conduct the appropriate responses efficiently. The nervous system is characterized by its ability to respond to stimuli with high speed and short duration. Complicated chains of interconnected neurons are necessary for the transmission of transient impulses, together with the highly localized production of chemicals such as adrenaline and acetylcholine which are rapidly destroyed. The endocrine system uses circulating body fluids to carry its chemical messengers to more or less specific target organs. There chemicals take time to build up to an effective concentration, and consequently must have a longer biological life than chemicals of the nervous system before they are eventually destroyed or excreted. Hormones are consequently well suited to exert their effects over extended periods of time, and endocrine system controls long-term processes within the body. Thus the endocrine system, when compared to the nervous system, is involved in responses that are slower and long lasting. Since the nervous system is the sole sensing arm of this reflex, the endocrine organs can be referred to as effector units of the nervous system, the link between the two is therefore the seat of integration. Thus, in all metazoa the nervous and endocrine systems so coordinate the activities of various organ and tissue in the body that the animals function as individuals.

Why animals have both nervous and endocrine systems, each performing a coordinatory role, is a matter of considerable interest. The nervous system makes possible the rapid adjustment of internal processes to environmental changes. Impulses are transmitted and are channelized and directed specifically towards particular loci in the organism. As organism evolved, it became imperative that the muscular system in particular be perfected so that quick coordination is possible. The swiftness required in adjustment of this is far beyond the power of a purely endocrine mechanism. Hormones or similar types of chemical coordinators have to be released by the organs that synthesize them and be transported by the circulation and

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transmitted through the tissues before reaching their appropriate target organs. Many of the hormone molecules are large and complex and it is probable that they pass slowly through the walls of blood vessels. Thus the two systems are functionally interrelated, one is primarily concerned with rapid adjustments and the other with processes that require duration rather than speed. It must not be supposed that the nervous system functions quite independently of the endocrine system. But it is likely that central nervous activity in most animals is strongly affected by hormones. For example, a mature female grasshopper will move towards and mate with a courting male. An immature female avoids, and will even fight with male if male persists in courtship. The hormone compliments of the two females cause their central nervous system to interpret the same information differently and to initiate quite opposite reactions. But the reverse is also true, i.e. hormone production and release is dependant upon the nervous activity. Almost all the animals have to respond developmentally to environmental changes throughout the year. In unfavourable conditions they undergo hibernation or migration or overcome them by other changes in behaviour or physiology. In favourable seasons most of the advantage is taken for rapid development and multiplication. Even slight fluctuations, such as shortage of food or the absence of suitable mates can have drastic effects upon development. The colour change in many crustaceans is brought about by alternations in the shade of their immediate environment. Similarly the act of mating in a female insect can accelerate the development of her egg. The change in day length of a day can control the on-set of metamorphosis in annelids. All these developmental and physiological responses result from changes in the concentrations of circulating hormones caused by nervous impulses originating in the stimulation of particular sense organs. Thus the nervous and endocrine systems are strictly interdependent.

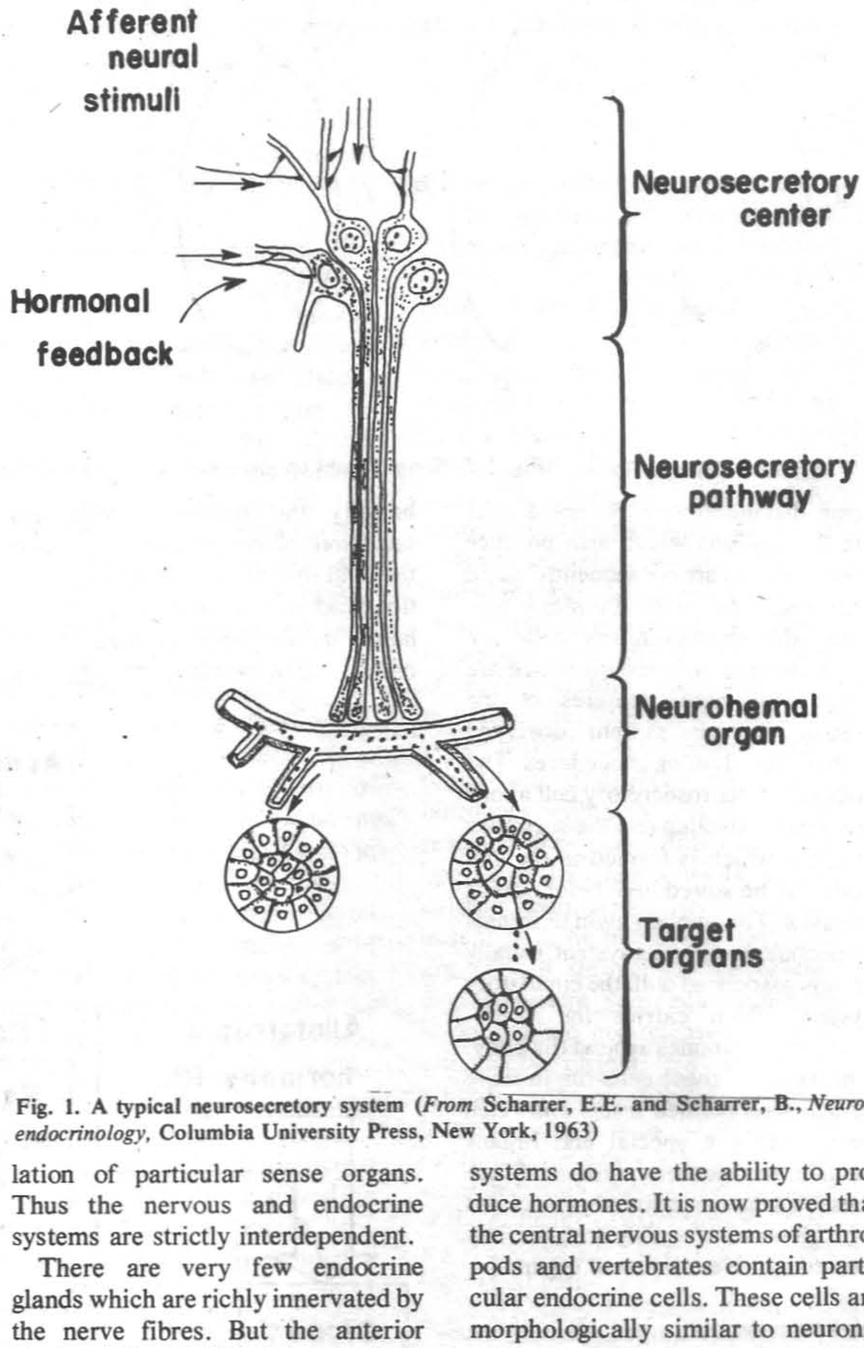

Fig. 1. A typical neurosecretory system (*From* Scharrer, E.E. and Scharrer, B., *Neuroendocrinology*, Columbia University Press, New York, 1963)

There are very few endocrine glands which are richly innervated by the nerve fibres. But the anterior pituitory gland which has been long known to produce a number of hormones and controls the activities of other endocrine glands contains very few nerve fibres. The question then is : How the nervous activity controls endocrine functions. In view of more recent observations, opinions about the possible endocrine function of nervous tissue have been completely reversed. It is generally now accepted that the nervous systems do have the ability to produce hormones. It is now proved that the central nervous systems of arthropods and vertebrates contain particular endocrine cells. These cells are morphologically similar to neurons, with axons, dendrites, nissl bodies and neurofibrillae. They are also able to transmit nervous impulses, but they differ from other neurons in two important respects; their axons do not innervate effector organs such as muscles, nor make synaptic connections with other neurons, and they manufacture materials often visible in stained sections of nervous tissue, which are released from the ends of the axons and exert a biological effect

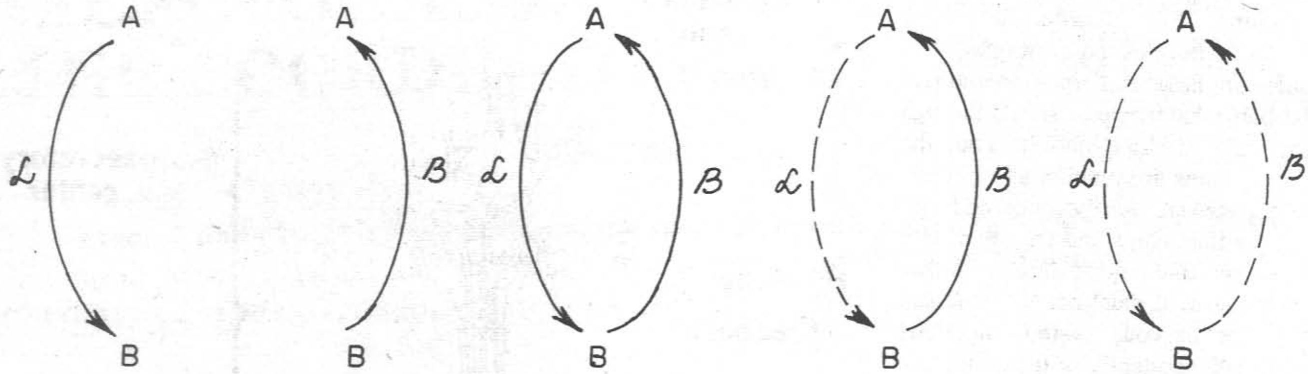

Fig. 2. Different phases of hormonal feedback (*After* Scharrer, 1963)

some distance away. So these cells are the neurons which also produce hormones and are consequently called neurosecretory cells. In many animals, the neurosecretory cells are often clumped into groups which are very conspicuous features of the central nervous system observed with proper staining procedures. The ends of the neurosecretory cell axons are usually swollen and the secretory material which is formed in the cell body can be stored here before being released. The swollen axon terminals lie outside the nervous system, usually closely associated with the circulatory system which carries the neurosecretory hormones around the body. The axons of these cells run in more or less well defined tracts and often terminate in a special end organs outside the nervous system. Since these structures are directly associated with blood vessels, they are generally termed as "Neurohaemal organs".

Neurosecretion

The distinction between the endocrine and nervous systems has diminished in recent years. The concept of the two systems working together to provide the organism with an integrative network has emerged. This has been favoured by the observations that the nerve cells synthesize, transport and secrete chemicals, which is broadly the definition of neurosecretion. Nerve cells generally play the dual role of conduction of excitation and secretion of such neurohumoral materials or neurotransmitters, e.g. acetylcholine, adrenaline, noradrenaline and 5-hydroxy-tryptamine which have important roles at interneuronal and neuromotor junctions. Since our concern is not with this aspect of neurosecretion, it will not be discussed here. Bragmann,

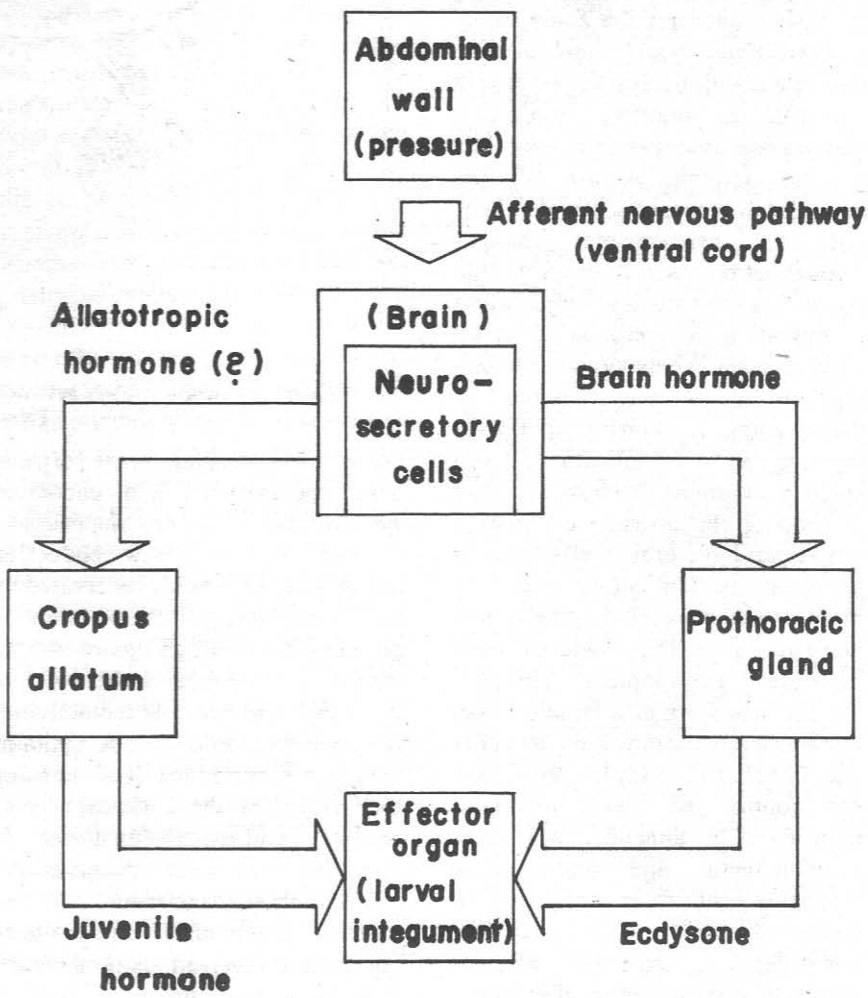

Fig. 3, Neuroendocrine control of moulting in insects (*After* Scharrer and Scharrer, 1963)

Hanstrom and the Scharrers have used another concept of neurosecretion which is most commonly accepted. This concept refers to a nerve cell containing prominent, stainable inclusion which appears to represent hormonally active secretory material, synthesized within the cell body, often transmitted via an axon to be released from the cell at some distance from the site of the synthesis and remaining active for longer period of time. Neurosecretory cells are essentially similar in both invertebrates and vertebrates, although, it is possible that the invertebrate cells may lack dendrites and it is not yet definitely proved that they can transmit nervous impulses. The material released from the neurosecretory cells is largely protein and reacts histologically and histochemically in much the same way whether it is produced by invertebrate or vertebrate neurosecretory cells. The electron microscope has provided us an ultrastructure of the neurosecretory cells. The basic neurosecretory product, the elementary neurosecretory granules, appear to vary in electron density, are membrane bounded, average between 1,000 Å and 3,000 Å in diameter and have their origin in the golgi apparatus of the neurosecretory cells. Knowles suggested two categories of neurosecretion, common in both vertebrates and invertebrates, which appears at the ultrastructural level: Type A with granules greater than 1,000 Å in diameter and peptide in nature and Tvpe B with granules less than 1,000 Å in diameter and with a nonpeptide or possibly an amine secretion. Type A is represented by the more commonly reported category of neurosecretion (Fig. 1.)

Some neurosecretory cells produce electron-transparent vesicles both in invertebrates and vertebrates. The dense spheres originate in golgi apparatus of the cell bodies in a manner similar to protein droplet formation in other endocrine and ordinary gland cells. In vertebrates the protein material synthesized by neurosecretory cells is called neurophysine which is the actual carrier of hormones. This is true of all vertebrate neurosecretory cells, but whenever the same applies to all invertebrate cells neurosecretion is problematical.

The endocrine organs are divided into two categories : those which are derived from embryonic ectoderm, mesoderm and endoderm layers, are called epithelial endocrine glands, and those which are derived from nervous tissue. Except the adrenal medulla and posterior pituitary all the endocrine glands and tissues of typical vertebrate are included in the first category. The adrenal medulla and posterior pituitary which developed from a transformed synaptic ganglion and of the brain respectively are therefore included in second category. But now it is confirmed after investigation that posterior pituitary is a neurohaemal organ as groups of neurosecretory cells are found in hypothalamus of the brain. Thus the posterior pituitory is quite a different endocrine organ from the adrenal medulla. In some vertebrates a second major neurosecretory system is situated at the posterior end of the spinal cord which is termed as caudal neurosecretory system. The functional significance of the caudal neurosecretory system remains obscure, but there are suggestions that its secretion may be involved in sodium exchange and gas metabolism.

In the vertebrate animals, epithelial organs developed from transformed nerve ganglia and neurosecretory cells often with well formed neurohaemal organ are all present. Even in complex animals like the arthropods, the number of epithelial endocrine glands is much less than in the vertebrates, and in most other invertebrate groups they are absent altogether. So the endocrine mechanisms in the invertebrates are usually simpler than the vertebrates. Because of the small number of epithelial endocrine glands in invertebrates, neurosecretory mechanisms assume great importance. However, many problems are associated with the determination of the function of neurosecretory system.

The classical endocrinological experiments to determine the functional aspects of neurosecretory system involves the removal of a suspected endocrine gland followed by its subsequent reimplantation at a different site in the body. If the consequences of removal are reversed and brought back to normal on reimplantation, then it is established that a hormonal mechanism is involved. But when a neurohaemal organ is removed, the cut ends of the neurosecretory axons may still release a hormone, sometimes in an uncontrolled manner. There is a possibility of regeneration of a new neurohaemal organ, so that the effects of deficiency of neurosecretory hormones may not be severe. When neurosecretory cells which supply neurohaemal organ are destroyed, the stored hormones within the organ may be released for some time after the operation. In some animals, a well defined neurohaemal organ may be absent, but the neurosecretory cells are present throughout the central nervous system. Some neurosecretory hormones are not released into the circulatory system, but are transported axonally directly to their target organs. It is rather difficult to determine the exact function of such neurosecretory mechanism because of the difficulty of extracting and testing biological materials from individual cells.

Neuroendocrine integration

The meaning of the term "Neuroendocrine integration" can be best explained by the following hypothetical situation. Suppose the endocrine organ 'A' after stimulation releases a hormone α, then its increasing titer in the blood stimulates endocrine organ 'B' which produces and releases hormone β. As hormone continues to stimulate organ 'B', the increasing blood concentration of hormone β

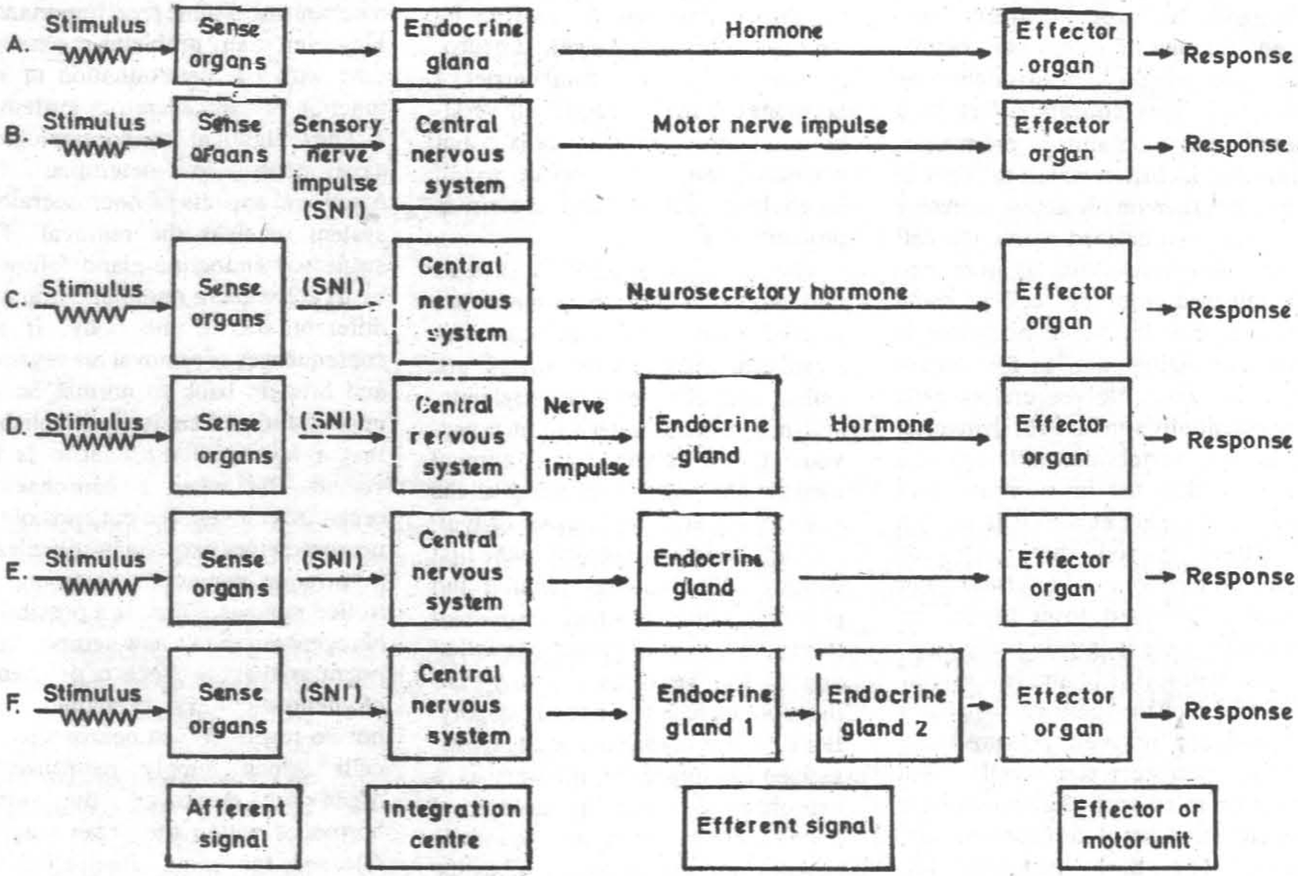

Fig. 4. An expansion of the reflex arc showing six possible means of activating a motor unit following the receipt of a stimulus by a sensory organ (*After* Frye, 1967)

begins to exert an inhibiting effect on organ 'A'. Organ 'A' reduces its output and naturally stops to release hormone α. Thus hormone β not only serves its particular function but also regulates its own production by its inhibitory effect on again 'A' (Fig. 2).

Here the environmental condition may affect in such a way that either organ 'A' should continue to stimulate organ 'B' irrespective of the blood titer of hormone β or should stop releasing its hormone although organ 'B' may have hardly begun to respond to stimulus of α. In order to accomplish such an adjustment, the feedback cycle is necessary. This point can well be illustrated by the control of ovarian function in mammals. The mechanism for release of gonadotrophins was originally conceived as a simple feedback of gonadal steroids to the pituitary. But, if this was the only determining factor, then external and internal conditions such as photoperiods, availability of food, social contact, etc. could not affect the reproductive cycle. There must be channels through which these modifying influences enter the control system and become integrated with the ovarian feedback mechanism. This integration can take place only in the central nervous system. So the ability of an organism to receive environmental signals, to respond to those which are important, to disregard the irrelevant and less important ones, and to retain normalcy throughout the body is due to integrative action of the central nervous system. This essentially involves three interrelated units: afferent pathways, integrative centres and efferent pathways.

1. Afferent pathways. Afferent pathways are known to play a very important role in control of endocrine functions. The receptor cells in the body are the prime movers in any reflex arc. They send their signals by way of afferent axons into a particular ganglion. This sense of reception can originate in special sense organs like photoreceptors, chemoreceptors and acoustic apparatus or also from touch, pain and temperature receptors. Retinal fibers of the eye, for example, carry impulses resulting from the increase of total illumination in spring, which in birds stimulates gonadal growth. Another important source of stimuli for the release of hormones controlling reproductive function lies in the olfactory apparatus. Stimuli may also result from changes in the internal environment, i.e., pH, osmolarity, chemical composition of blood or from hormonal feedback. In insects also, a considerable information has been obtained regarding the control of endocrine function by afferent nervous pathways. For example, in nymphs of the blood sucking hemipteran *Rhodnius* sp., initiation of the moult cycle depends upon nervous stimulation having its origin in stretch receptors in abdomen. After a meal of blood in a sufficiently large quantity, the receptors are activated and through the ventral nerve cord stimulate the neurosecretory cells of the brain to produce their appropriate secretions. In certain species of cockroaches tactile stimuli resulting from mating and proprioreceptive impulses caused by pregancy reach the brain by way of the ventral nerve cord (Fig. 3).

2. *Integrative centres.* By way of neural and vascular routes nervous and chemical afferent stimuli converge on the central nervous system, which in turn transmits excitatory or inhibitory signals to the target organs. For example, afferent nervous, hormonal and direct stimuli, converge on the nerve centers which issue efferent messages concerned with the respiration, hunger, thirst, temperature control and many other basic functions. With the changes in CO_2 content, glucose concentration or temperature of the blood, the neurons get directly stimulated. Nervous impulses originating from the peripheral receptors have access to these centres via synapsing neurons. The sum total of the information received results in decision to increase or decrease respiratory rate, to sweat or to shiver, to store or to mobilize glycogen. The portion of the nervous system which receives such impulses and translates them into effective nervous or hormonal output signals has been called final common pathway. The neurosecretory cells constitute the link between central nervous system and organs of internal secretion. Their dual character as nerve and gland cells enables them to receive nervous impulses from other neurons and stimulate or inhibit the organs of internal secretion by dispatching chemical messages.

3. *Efferent pathways.* Neurohormones may act either directly on the target organ or they may first act on endocrine tissue which in turn influences the target organ. Frye has given six pathways to show possible relationships between neural hormonal components (Fig. 4).

First order of neuroendocrine reflex

Here the neurosecretory cells exert direct control over target organs. Inhibition of gonadal maturation in annelids and crustaceans and stimulating smooth musculature or promoting water conservation by the kidney in vertebrates are the examples of first order of neuroendocrine systems. The agents are released from neurohaemal organ into general circulation, proportionately in large quantities to maintain effective concentration. The possibility also exists that the stimuli may act directly on neurosecretory cells within the central nervous system, which would make scheme C more like scheme A (Fig. 4).

Second order of neuroendocrine reflex

The incorporation of one non-neuronal endocrine organ between the neurosecretory cells of the central nervous system and the final target organ represents this second order reflex. For examaple, in case of *Rhodnius* sp., as described previously, the neurohormones influencing the prothoracic glands and corporallata to subsequent release of ecdysone and juvenile hormones respectively illustrate the second order of neuroendocrine reflex. This additional non-neuronal structure generally is in close association with the neurosecretory cells or processes of such cells. Such incorporation of non-neuronal structure facilitates efficient transfer of information which might

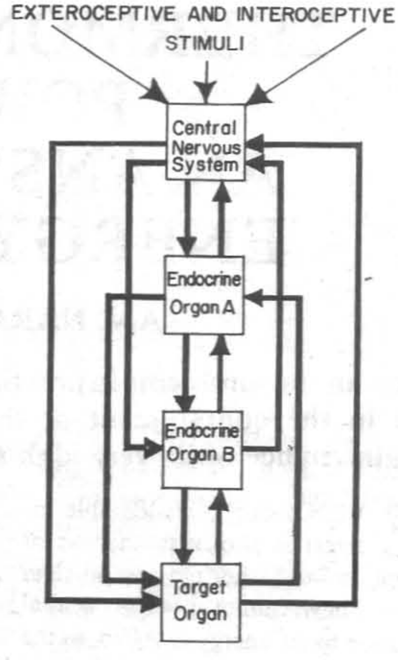

Fig. 5. Possible neuroendocrine interactions to include the First, Second and Third order systems

not be the case if the active components entered the vascular system directly.

Third order of neuroendocrine reflex

The incorporation of two non-neuronal endocrine organs between the neurosecretory cells of the central nervous system and the final target organ illustrates this third order reflex (scheme F in Fig. 4). For example, the role of the anterior pituitary in the case of adrenal cortical stimulation. The corticotropin releasing factor (CRF) produced by the hypothalamic neurosecretory cells does not enter the general circulation to act directly on the adrenal cortex. It is carried by hypothalamic portal vessels to the adenohypophysis where it stimulates the release of adrenocorticotropic hormone (ACTH). The ACTH reaches the adrenal cortex causing it to build up its secretary apparatus and to release corticoids (second order of neuroendocrine reflex). Nor is this the limit of such sequences but in the third

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