I. General Aspects of Endocrinology

HANS BÜRGI

A. Introduction

Hormones are chemical messengers which are dissolved in extracellular fluid and carry information between cells*. Within any single cell, information is transmitted through chemical compounds in a similar manner. Such intracellular messengers include enzymes, allosteric ligands and proteins, certain ribonucleic acids and deoxyribonucleic acids. It is noteworthy that deoxyribonucleic acids can also store information, a feature which is lacking in the endocrine system. The function of hormones might be compared to that of nerves, which also convey information from one cell to another.

![Diagram of flow of information](image)

Fig. 1. Schematic representation of the flow of information within an endocrine cell and from there to the receptor cell. The dashes indicate a feedback loop. Abbreviations: RNA: ribonucleic acid; DNA: deoxyribonucleic acid

In contrast to the endocrine system but like the intracellular genetic system, the nervous system is also capable of storing information.

* This definition is based on physiological considerations and does not include hormones or their pharmacological derivatives as used for therapeutic or diagnostic purposes. A similar "operational" definition of hormones has recently been exhaustively discussed by Vallotton (1969).
distant. Hormones which diffuse only locally in the interstitial fluid surrounding an endocrine cell are called tissue hormones.

Hormone molecules transfer their information through contact with a receptor at the target cell. They thereby regulate certain chemical or physical processes within the receptor cell which finally result in known biochemical and clinically evident hormonal actions. In many cases the information contained in the hormone is reconverted at the cell membrane into an intracellular second messenger which in turn controls a process within the cell. In this manner information issued by the endocrine cell eventually reaches its destination. However, the flow of information in the organism does not cease at this point. Processes may be triggered in the target cell which lead to the formation of feedback loops. Under the influence of a hormone a receptor cell may release greater or smaller amounts of a chemical compound (e.g. a metabolite or another hormone) into the extracellular fluid, hereby informing the original endocrine cell that it has received and executed the instruction. Frequently, in a negative feedback, this will inhibit the endocrine cell from issuing the same information, i.e. from secreting more hormone. Fig. 1 shows a simplified representation of the flow of information from the endocrine cell to its receptor and back to the endocrine cell of origin. The individual steps in the transfer of information by hormones will now be discussed in detail and illustrated by typical examples.

B. Endocrine Genetics

Hormones are of great interest to the geneticist primarily because certain diseases are known to be caused by inherited deficiencies of specific hormones. Examples among the protein and peptide hormones are the inherited deficiencies of antidiuretic hormone and of growth hormone. Whether diabetes mellitus is due to an inherited disorder of insulin biosynthesis is still controversial. In addition, several endocrine disorders are caused by an inherited deficiency of the enzymes necessary for the biosynthesis of non-protein hormones. Examples are the various adrenogenital syndromes and certain forms of congenital hypothyroidism. Inherited failure of the target organ to respond to its corresponding hormone is the cause of pseudo-hypoparathyroidism and renal diabetes insipidus.

Patients with the syndrome of multiple endocrine adenomata suffer from an inherited tendency to develop tumors in various endocrine glands. Certain disorders of the thyroid gland, such as thyrotoxicosis, Hashimoto's thyroiditis, and primary myxedema, all of which appear to be associated with autoimmune processes, show a familial incidence without clear-cut genetic transmission.

Other endocrine diseases, for example, Turner's syndrome and Klinefelter's syndrome, are due to chromosomal disorders. These syndromes have provided important information regarding the function of sex chromosomes.

It may be of interest to the biochemically oriented geneticist to know that hormones were among the first proteins to have their amino acid sequences fully elucidated. Surprisingly, certain hormones with very different actions were found to be chemically closely related. Thus, large parts of the ACTH molecule are identical to the α-MSH molecule and a whole subunit of the TSH molecule is identical with a subunit of the LH molecule. Such close similarity between two proteins is probably the end result of gene duplication, an important mechanism by which new proteins are acquired in the course of evolution.

C. Biosynthesis of Hormones

Research on the biosynthesis of protein hormones has long been hampered by the lack of suitable isolated tissue preparations and, in particular, of corresponding cell-free systems. However, one may assume that protein hormones are synthesized at the ribosomes according to the "classic" concepts of molecular biochemistry. Insulin is the protein hormone whose biosynthesis has been most fully studied. The linkage of the two peptide chains of insulin by two disulfide bridges represents a particular biochemical problem. The earlier view that the two protein chains were separately synthesized and subsequently joined by the disulfide bridges no longer seems tenable. The investigations of STEINER (1967) in both man and rat demonstrated a single-chained insulin precursor—proinsulin—containing both the A and the B chains of insulin. The amino acid sequence of proinsulin has been worked out recently by CHANCE (1968). The two-chained insulin molecule arises through enzymatic removal of a peptide, the connecting or C-peptide, from the proinsulin molecule. The mechanism suggested by STEINER and CHANCE for the biosynthesis of insulin is shown in Fig. 2. Whether analogous "pro-hormones" also exist for other protein hormones remains to be investigated. Strictly speaking, thyroglobulin could be considered the pro-hormone of thyroxine, since thyroxine is an