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An Introduction to Receptors and Receptor Disorders (40608)

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The aim of this symposium is to sketch in outline the role of receptors in disease states. Rather than attempting a comprehensive review, we shall present selected examples to illustrate broad principles: the role of insulin receptors in disorders of glucose tolerance and insulin sensitivity, estrogen receptors in breast cancer, and acetylcholine receptors in myasthenia gravis. They represent the polypeptide hormones, steroid hormones, and neurotransmitters, respectively. This choice causes us to neglect other important applications such as TSH receptors in Graves' disease and the work on receptors for other polypeptide hormones such as glucagon, MSH, TRH, LH-hCG, and prolactin; receptors for other systems such as catecholamines, opiates, prostaglandins, and lipoproteins; and receptors for malaria parasites and viruses, all of which have their receptors on the cell surface. Also excluded have been the roles of androgen and thyroid receptors in hormone-resistant states and of glucocorticoid and other steroid receptors in leukemias and other malignant disorders (1–4).

Biological role of receptors. For a ligand to produce its biological effect it must first bind to its specific receptors on a target cell. The receptor serves two major functions. First, the receptor must recognize the biologically active moiety by binding it. Second, the combination of ligand with receptor initiates the biochemical events that lead to the biological action of the specific ligand system. In the case of hormones, the ligand has no function in the absence of receptor. Whether the receptor has function in the absence of hormones (i.e., a basal activity) is as yet unclear. In addition to its fundamental roles of recognition and activation, the ligand–receptor interaction often participates in other biological functions. Some of these additional functions for the interaction of insulin with its receptor are listed in Table I.

Information transfer. While it is clear *in vivo* that the ligand and cell receptor are both necessary for the system to function, it is worthwhile to consider the relative role of each in transmitting information to the cell (Table II). For some systems, such as sperm and egg, both moieties contribute approximately equal amounts of information. With other systems, the information is in the ligand, and the receptor serves only to concentrate the ligand, process it, and expedite its translocation to its site of action. Thus in the case of low-density lipoproteins (LDL), cholesterol within the LDL molecule is the signal to the cell. The receptor acts to get LDL into the cell where the LDL is processed to yield free cholesterol. If cholesterol is put into the cell by some extra receptor mechanism, the net biological effect is the same. Similarly, toxins such as cholera toxin and diphtheria toxin are enzymes. Binding of toxin to receptor leads to activation of the enzyme and its entry into the cell where the toxin acts. Introduction of the activated toxin by mechanisms that bypass receptor lead to the characteristic effects of the toxins. Thus the signal is entirely within the ligand.

In other cases the full program of information is within the receptor, and the ligand acts solely to cause the receptor to express its program. For example antibodies directed against the receptor for insulin mimic all of the biological effects of insulin acting on the insulin receptor (5, 6). The antibody to receptor (in the absence of insulin) stimulates transport of glucose and amino acids (immediate effects), activation of glycogen synthase and inactivation of phosphorylase (intermediate effects of insulin), and synthesis of lipoprotein lipase (a delayed insulin effect).

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TABLE I. FUNCTIONS OF THE RECEPTOR–HORMONE INTERACTION

A. Fundamental
1. Recognition
2. Activation

B. Additional
1. Reservoir for plasma hormone
2. Regulate degradation of hormone
3. Regulate degradation of receptor
4. Regulate receptor concentration and receptor affinity
5. Crosslink and translocate hormone–receptor complexes
6. Regulate postreceptor events

TABLE II. INFORMATION TRANSFER

A. Hormone + receptor $\rightleftarrows$ hormone–receptor complex $\rightarrow$ activation
B. Where is the "*information*" for the activation—H?? R?? HR??
C. Examples of ligand–receptor systems
1. Both moieties contribute about equally—egg and sperm
2. Information is in the ligand; receptor acts to concentrate, process, and/or translocate the ligand to an intracellular site
a. Toxins: cholera, diphtheria, ricin
b. Low-density lipoproteins
c. Lysosomal enzymes
d. Viruses
3. Information is in the receptor; ligand acts to bring out the program from the receptor
a. Insulin
b. IgE
c. (Thyrotropin)
d. (Acetylcholine)

That antibodies (and probably concanavalin A), which bind to regions of the receptor outside of the insulin binding site, can initiate the characteristic panoply of insulin effects suggests very strongly that all of the information is in the receptor, and the sole function of insulin is to cause the receptor to express itself. Similar reasoning applies to studies of the IgE receptor where again antibodies to the receptor can replace the normal ligand, which is antigen linked to IgE (7, 8). Though less well studied in this regard, two other examples where the receptor appears to contain the fundamental information are the receptors for acetylcholine and for TSH.

Studies of this type which dissect the role of ligand and receptor in the process of information transfer are important in understanding the mechanism of disease and potentially have important therapeutic consequences. For example, in patients who are insulin deficient, the current therapeutic strategy is now focused on improved methods of insulin delivery such as islet-cell transplantation and automated systems for insulin infusion. If the receptor has all of the information, then the hormone can be bypassed and a much broader range of agents that act on receptor can be surveyed as potential substitutes for insulin.

Receptors in endocrine systems. As shown in Fig. 1, hormone released from the gland travels in the plasma to target cells throughout the body where it binds rapidly to a finite number of receptors on the cell. Hormones that are lipid soluble such as iodothyronines, steroids, and vitamin D derivatives quickly (freely?) cross the plasma membrane. Their receptors are inside the cell, and their primary site of action is in the nucleus (Table III).

The peptide hormones, which represent at least 80% of all hormones, and the catecholamines are water soluble and do not easily cross the lipid barrier posed by the plasma membrane of the cell. Their specific binding sites are on the outer surface of the plasma membrane (9) (Table III). The receptors which contain the specific binding sites are integral membrane proteins (which cannot be freed from the membrane except by the use of detergents). The combination of receptor with hormone generates a transmembrane message, which leads to the activation of

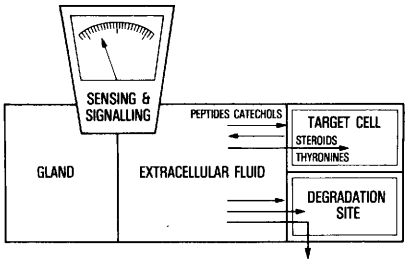

FIG. 1. Schematic diagram of an endocrine system. Sensing device(s) signals the gland to release hormone into the extracellular fluid in which it travels to reach cells throughout the body. Hormones that are lipid soluble such as steroids, 1,25$(OH)_2$-vitamin D_3, and iodothyronines traverse the plasma membrane of the cell and interact with receptors that are intracellular. The peptide and catecholamine hormones, which are water soluble and do not steadily traverse the lipid barrier of the cell membrane, interact with their receptors on the outer surface of the cell.

TABLE III. CLASSIFICATION OF HORMONES

Chemical class	Percentage of all hormones	Solubility	Receptors	Postreceptor
Peptides Catecholamines	≧80 ≦5	Polar	Cell surface	Second messenger
Steroids (and sterol) Iodothyronines	≦15 ≦5	Nonpolar	Intracellular	Nucleus

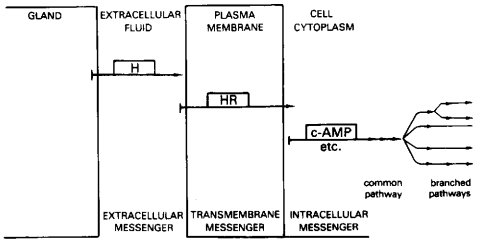

FIG. 2. Cellular events in the action of peptide and catecholamine hormones. The hormone (H) is the extracellular messenger, carrying the signal from the gland to the outer surface of the target cell, where it combines with specific receptors (R) to form hormone–receptor complexes (HR). The latter initiates a transmembrane message; the nature and form of the transmembrane messenger are unknown. The next step for many of these hormones is activation of adenylate cyclase at the inner surface of the plasma membrane, which generates cyclic AMP (cAMP), a soluble intracellular messenger that activates specific protein kinase(s). This sequence of intracellular events is designated "common pathway." The kinase is thought to activate and inactivate many intracellular proteins, which leads to the many biological effects characteristic of a given hormone in a single target cell, designated "branched pathways." For hormones that do not activate adenylate cyclase, the "common pathway" is unknown but thought to be of similar general design.

intracellular processes (Fig. 2). The nature of the transmembrane messenger(s) is not known. The earliest known intracellular event for many peptide hormones and for β-adrenergic catecholamines is activation of adenylate cyclase, followed by production of cyclic AMP and activation of cyclic AMP-dependent protein kinase(s). All (or most) of the effects of these hormones are thought to be the result of action of the specific kinase(s). For hormones such as insulin, prolactin, growth hormone, and the α-adrenergic catecholamines that do not act via the adenylate cyclase–cAMP kinase pathway, the nature of the early intracellular events is unknown, but it has been widely assumed that the design of the system is similar.

Many receptors for nonendocrine systems (neurotransmitters, LDL, prostaglandins) are membrane proteins with binding sites on the cell surface and are similar in many respects to receptors for peptide and catecholamine hormones. Exceptions thus far are receptors for cholera toxin which appear to be GM_1 gangliosides on the cell surface and possibly receptors for other microbial products or agents.

Quantitative aspects of the hormone–receptor interaction. Free hormone (H) in the plasma or extracellular fluid binds reversibly to receptors (R) to form hormone–receptor complexes (HR) (Table IV). The concentration of these complexes, [HR], determines the magnitude of the signal to the cell. The biological effect is some function, f, of the concentration of HR, which in turn is a function of hormone concentration [H], receptor concentration [R], and the affinity of receptor for hormone, K. Since all three ([H], [R], and K) are partners in determining the signal rate to the cell, the signal will vary in response to changes in any of the three determinants (Table IV). While it has been clear that hormone concentrations fluctuate rapidly *in vivo*, it has become clear only recently that receptor concentration and affinity both fluctuate in response to biologically relevant stimuli and that these wide and often rapid responses contribute greatly in determining the magnitude of the biological response observed.

Biologically relevant fluctuations in receptor affinity and concentrations. Historically pharmacologists and endocrinologists, in their use of biological systems, often selected conditions to minimize or obscure changes in target cell sensitivity including changes in the receptor. Thus the pharmacologists who wished to study agonists and antagonists wished to have the biological response that they observed reflect only the effect of alterations in the nature of the ligand or its concentration. Similarly, the endocrinologists in their study of

TABLE IV. THE INTERACTION OF HORMONE WITH RECEPTOR

1. The primary interaction

$$H + R \rightleftarrows HR$$

H = free hormone
R = free receptor
HR = hormone–receptor complexes
R_0 = total receptors (R + HR)

2. The equilibrium constant (K_a) for this reaction

$$K_a = \frac{[HR]}{[H]\,[R]}$$

3. The biological effect (E) is some function (f) of the strength of the signal to the cell; the signal strength is directly related to [HR].

$$E = f([HR])$$
$$= f(K[H][R])$$
$$= f\left(\frac{K[H][R_0]}{1 + K[H]}\right)$$

hormones set conditions so that the biological response they observed reflected only changes in the concentration of hormone. Thus bioassays for drugs, hormones, and other ligands depend entirely on the ability of the investigator to fix the responsiveness of the target cell. That so few bioassays work well and require such meticulous attention to methodological detail attest to the fact that target cells by their nature are not fixed targets but rather change their responsiveness rapidly in response to numerous stimuli. Given the natural propensity of target cells to regulate their responsiveness so quickly and so widely makes it clear, retrospectively at least, why bioassays require such herculean efforts to make them perform adequately.

While any biochemical step within the target cell can be responsible for the changes in responsiveness, recent studies make it clear that the first step, the binding of ligand to receptor, is frequently affected (10–19). In the case of the receptor for insulin, numerous biologically relevant events produce changes in the receptor (Table V). Growth rate, differentiation, and environmental conditions can have profound effects on the receptor. Dietary composition, total calories, timing of meals, and exercise have major effects at the level of the receptor concentration or affinity. The homologous ligand itself acts to regulate both concentration and affinity of its own receptor; regulation of receptor concentration is a regulatory event that requires cellular events beyond the receptor whereas regulation of receptor affinity appears to be a physicochemical process intrinsic to the receptor that can be reproduced fully with detergent-solubilized receptors. Other (heterologous) hormones and drugs can affect target cell receptors for insulin and thereby alter target cell sensitivity to insulin. A condensed list of these regulators is presented in Table V. Given that the receptor is at the interface between the inside and outside of the cell, it is reasonable retrospectively that it is responsive to signals from both the external and internal environments of the cell.

TABLE V. BIOLOGICALLY RELEVANT REGULATORS OF AFFINITY AND/OR CONCENTRATION OF INSULIN RECEPTORS

1. Exercise	7. Age
2. Meals	8. cAMP
3. Diet	9. pH
4. Insulin	10. Ketones
5. Other hormones	11. Sulfonylureas
6. Growth and development	12. Anti-receptor antibodies

Historical perspective. The concepts of hormones and of receptors were both introduced in the last quarter of the 19th century and were clearly formulated during the first decade of this century. During the next 60 to 70 years the study of hormones advanced rapidly while that of receptors lagged. The natural advantages of hormones, some of which are cited in Table VI, explain some of this disparity in progress. Basically, the hormone was easier to study.

The dominance of hormone over receptor (and target cells) has been so great that endocrinology, instead of being the study of

TABLE VI. NATURAL FACTORS THAT FAVORED PROGRESS WITH HORMONES

	Peptide hormones	Cell surface receptors
Highly concentrated in a localized region	Yes	No
Soluble in aqueous solvents	Yes	No
Biological effect when introduced *in vivo* and *in vitro*	Yes	No
Present in blood	Yes	No

endocrine systems, has been viewed as the study of hormones. Likewise endocrine disorders have been viewed as diseases of hormones. Clearly if an endocrine system is deranged, any one of the steps can be at fault. Yet most disorders have been viewed simply as due to hormone excess or hormone deficiency.

When the biological effect of a hormone was deficient, hormone deficiency was blamed. Only later did it become clear that in many disorders hormone was present at normal or supernormal concentrations and that the target cell was defective. Thus hypocalcemia due to parathormone deficiency was recognized long before target cell resistance to the hormone (pseudohypoparathyroidism); polyuria due to vasopressin deficiency before vasopressin-resistant states (nephrogenic diabetes insipidus); dwarfism due to growth hormone deficiency before growth hormone-resistant (Laron-type) dwarfism; and failure of sexual development due to androgen deficiency before the hormone-resistant causes. In the examples cited, resistance to the hormone was complete or almost complete. In diseases where the effectiveness of the hormone was reduced but not absent, recognition of the defects were even slower to evolve. Thus with insulin resistance, the sensitivity of the target cell to insulin is reduced but not totally absent and therefore more subtle. (Total refractoriness to insulin may be fatal.)

Disorders of glucose metabolism. It has long been known that glucose stimulates the β-cells of the pancreas to release insulin which acts on target cells to promote glucose utilization and storage. However, only glucose could be measured so that the system was oversimplified—hyperglycemia was due to insulin deficiency and hypoglycemia was due to insulin excess. The dramatic response of diabetics to insulin administration and the similarity of patients with islet-cell tumors to symptoms of diabetics who received too much insulin strengthened this simple formulation. With the introduction of methods to measure insulin levels in blood, especially the radioimmunoassay, it became clear that only a minority of patients conform to this scheme (13). The diabetics who are truly insulin requiring are indeed insulin deficient but the majority of hyperglycemic patients are not absolutely insulin dependent and have normal or supernormal concentrations of circulating insulin (Table VII). Further, the insulin in these patients is biologically intact insulin. Conversely in patients with hypoglycemia due to islet-cell tumors, insulin levels were found to be inappropriately elevated, which conformed to expectations, while in many patients with low normal glucose or frank hypoglycemia, plasma insulin was noted to be low or unmeasurable (Table VII). Thus the radioimmunoassay for insulin, while it

TABLE VII. CONCORDANCE AND DISCORDANCE OF CIRCULATING HORMONE CONCENTRATIONS AND THE BIOLOGICAL STATE

	Hormone concentration subnormal or unmeasurably low	Hormone concentration normal or elevated
Biological response deficient	Concordant Insulin-dependent (juvenile type) diabetes (~20%)	Discordant Non-insulin-dependent (adult-type) diabetics (~80%) Growth hormone excess Glucocorticoid excess Uremia Syndromes of extreme insulin resistance
Biological response excessive	Discordant Non-islet-cell tumors Anorexia nervosa Growth hormone deficiency Glucocorticoid deficiency	Concordant Islet-cell tumors Infants of diabetic mothers

confirmed that hormone levels were concordant with biological observations in some patients, raised a paradox in most conditions—the hormone levels were discordant with the biological observations (Table VII). The introduction of methods to measure the receptor has resolved many of these apparent paradoxes. It was shown in many disorders of glucose metabolism, where hormone levels were discordant with the clinical state, that the receptor was altered and reflected the clinical state.

Receptor methods. The first attempts to measure receptor, reported 30 years ago, failed because it was not clear that the labeled hormone was biologically active, degradation of hormone and of receptor were not controlled, and it could not be shown that the observed binding of hormone to tissue was biologically relevant, i.e., nonspecific binding accounted for most or all of the binding (14, 15). Subsequent studies of this type suffered the same shortcomings.

The modern era of receptors began in the sixties when studies were aimed at overcoming these problems. For steroid hormones, the problem was somewhat simpler (16, 17). Tritiated hormones, prepared for other studies, were bioactive and therefore suitable for receptor studies. The receptors were soluble cytoplasmic components and therefore the well-developed techniques for studying the binding of two soluble components were applicable. However these methods were not applicable to the vast majority of hormones or to most nonendocrine receptor systems; the radioactive ligands available were unsuitable (i.e., of uncertain biological activity or inadequate specific activity), and the methods for dealing with membrane-bound proteins (receptors) were primitive.

The current methods for studying cell-surface receptors are based on the methods introduced for the study of ACTH and angiotensin binding to their specific receptors (18–22). The approach of the two pioneer groups were similar. Meticulous attention was given to preparing radioactive ligand at very high specific activity that retained biological activity. The receptor preparations were handled to minimize both nonspecific binding and degradation of hormone and receptor. Finally the binding of labeled hormone was shown to have the precise specificity of the biological system, i.e., bioactive analogs competed for binding in proportion to their biological potency, and irrelevant materials (e.g., other substances including other hormones) had no effect. These techniques have proved widely applicable to all other peptide hormones and catecholamines, as well as to neurotransmitters including the opiate-like agents, prostaglandins, lectins, toxins, lipoproteins, microbes, and other agents that have cell surface receptors (Table VIII).

Receptors and disease. With the introduction of methods to study receptors directly, most studies were focused on biochemical characterization of the systems. Breast cancer and leukemia as well as nonmalignant disorders were the first diseases where receptors were implicated as having an important role (22–27). Bullock and Bardin noted that an androgen-resistant state, testicular feminization in one strain of mice, is associated with a severe deficiency of androgen receptors (24). In the same year Kahn *et al.* found that insulin resistance in mice associated with hyperinsulinemia and obesity is characterized by a deficiency of insulin receptors (25). Since that time a wide range of androgen-resistant and insulin-resistant states in humans and in animals have been shown to be associated with receptor defects (6, 24–33). Further, the severity of the hormone resistance often correlated well with the severity of the receptor defect. Several treatments that improved the defects in insulin responsiveness were associated with improvements in the receptor. Conversely, heightened sensitivity to insulin and/or insulin deficiency were associated with increased binding of hormone to receptor, and correction of the clinical disorder correlated with correction of the receptor abnormality. Since that time, receptor defects have been found in other areas of endocrinology as well as in other nonendocrine re-

TABLE VIII. CELL SURFACE RECEPTORS

ACTH and *Angiotensin* → Other H →	Other surface receptors
Oxytocin	Toxins
Glucagon	Lectins
Insulin	Neurotransmitters
Growth hormone	Opiates
Gonadotropins	LDL
Catecholamines	Prostaglandins
Other	Other

ceptor systems, and many disease mechanisms that were poorly understood have become much clearer (31–37).

Quantitative versus qualitative defects. In some disorders, the receptor is absent or so severely deficient that the biological effect of the ligand is virtually nil (Table IX). Some of the hormone-resistant states, including some hormone-resistant malignancies, the homozygous form of familial hypercholesterolemia (34), and the resistance to one form of malaria are examples of this class (35). In other disorders, the receptor is present but the concentration or affinity of receptor is altered so that the effect of a normal concentration of the ligand produces a deficient or excessive response. The mechanisms for these alterations are numerous. Examples include most disorders of insulin responsiveness, other endocrine abnormalities, and the most common form of familial hypercholesterolemia.

In another group of disorders the mechanisms are more complex and involve a dysfunction of the receptor (Table IX). In a rare form of familial hypercholesterolemia, the receptor can bind the ligand but the receptor is defective; it does not concentrate in the coated pits on the cell surface and bound ligand is not internalized. In Graves' disease, antibodies to the TSH receptor cause the receptor to signal the cell in the absence of the normal ligand and without regard to normal control mechanisms (36). In myasthenia gravis, the antibody to the acetylcholine receptor alters receptor turnover and function (37). In several forms of insulin resistance antibodies to receptor not only impair the affinity of receptor for ligand but can also acutely mimic insulin action and can also chronically impair the sensitivity of the target cell to insulin at some site beyond binding of hormone to receptor. When the defect in the receptor is more than just a defect in binding, it is more difficult to detect and to unravel.

In addition to the situations where the receptor is abnormal quantitatively or qualitatively, there is a group of disorders due to defects in the nature of receptor design (Table X).

Disorders due to defects in receptor design (31–33). Ideally, each hormone should be a unique entity and have a unique set of receptors. This would confer absolute specificity on the system (Fig. 3, "Ideal"). In many cases the hormone is not truly unique chemically or in its binding to receptors; there is some limited degeneracy built into the system. Thus one hormone, in addition to its strong reactivity with its own receptors, may also react weakly (i.e., with much lower affinity)

TABLE IX. EXAMPLES OF DISEASES AND OTHER RELEVANT CONDITIONS RELATED TO RECEPTORS

A. Virtual absence of ligand binding to receptor
1. Androgen-insensitive states—several
2. Extreme insulin resistance in one case of leprachaunism
3. Other disorders with total refractoriness to hormone
4. LDL receptors in homozygotes with familial hypercholesterolemia
5. Duffy-negative human erythrocytes are resistant to vivax malaria

B. Decreased binding of ligand to receptor
1. Insulin-resistant states—many
2. LDL receptors in heterozygotes with familial hypercholesterolemia
3. Catecholamine receptors in asthmatics who receive adrenergic agents chronically

C. Increased binding of ligand to receptor
1. Heightened responsiveness to insulin in anorexia nervosa, growth hormone deficiency, glucocorticoid deficiency
2. Thyroid hormone increases catecholamine receptors
3. Estrogens increase oxytocin receptors
4. Estrogens increase progesterone receptors

D. Complex disorders involving receptors
1. Antibodies to TSH receptor in Graves' disease mimic TSH and cause hyperthyroidism
2. Antibodies to acetylcholine receptor are responsible for myasthenia gravis
3. Antibodies to insulin receptor in Type B extreme insulin resistance, ataxia telangiectasia, other immune deficiency states, NZO mice
4. Defective LDL receptor in one patient with familial hypercholesterolemia

E. Disorders of receptor design (specificity spillover)—see Table X

TABLE X. CANDIDATES AS DISORDERS POSSIBLY DUE TO DEFECTS IN RECEPTOR DESIGN—SPECIFICITY SPILLOVER

Clinical condition	Hormone in excess	Reacts with receptors for	To produce
Non-islet-cell tumors	NSILA-s (IGF-II)	Insulin	Hypoglycemia
Babies of diabetic mothers	Insulin	Insulin-like growth factors	Macrosomia
Untreated Addison's disease; Autonomous overproduction	ACTH	α-MSH	Skin darkening
Acromegaly	hGH	Prolactin	Galactorrhea, amenorrhea
Choriocarcinoma	hCG	TSH	Hyperthyroidism
Primary hypothyroidism in childhood	TSH	LH, FSH	Precocious puberty
Glucocorticoid excess	Hydrocortisone	Aldosterone	Hypertension
Hypertension of pregnancy; Essential hypertension	Oxytocin? Other nonapeptide?	Nonapeptide pressor	Hypertension

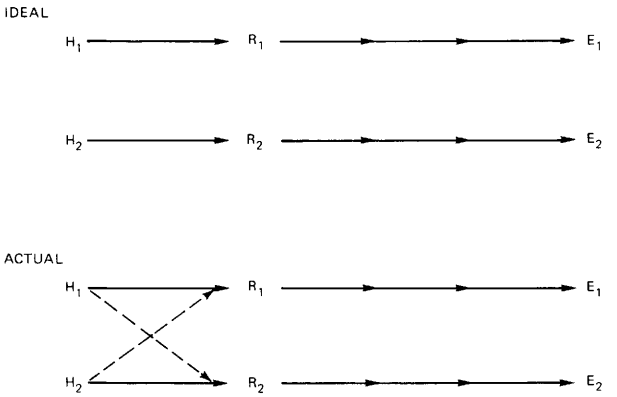

FIG. 3. Specificity in hormone–receptor interactions. In the ideal case, each hormone (H) has its own unique receptor (R) with which it combines to produce its specific series of biological effects (E) and has no affinity at all for receptors of other hormones. Actually one hormone (H_1), in addition to its strong reactivity (→) with its own receptors (R_1), can react with a weak but finite affinity (——→) with receptors (R_2) of a closely related hormone (H_2); high concentrations of H_1 can thereby produce its own characteristic effects (E_1) as well as those effects (E_2) characteristic of the related hormone (H_2).

with receptors of a closely related hormone (Fig. 3, "Actual"). Under ordinary circumstances the weak reactivity of a hormone for receptors of another may be of no consequence. However, when the concentration of the hormone is increased (as in states of hormone excess) the hormone may now act to stimulate this second pathway (i.e., to produce the biological response characteristic of the other hormone), in addition to stimulation of its own pathway (Fig. 4). The cross reaction of one hormone onto the receptor of another is not random (i.e., not "promiscuous") but each occurs only within the bounds of a well-defined family of closely related hormones and receptors (i.e., "incestuous").

Table X contains a list of diseases characterized by hormone excess in which one or more symptoms may be due to one hormone acting to stimulate the receptor for another (related) hormone (31–33). We have designated these kinds of disease manifestations as due to specificity spillover at the receptor. It should be emphasized that this general mechanism has not been proven; rather we have proposed this as a possible disease mechanism to provide a simple explanation for some unexpected manifestations of hormone excess. The validity of the concept can be tested experimentally. These suggested examples would add to the list of disorders where examination of a receptor provides a major advance in our understanding of disease process.

Summary. In the last decade reliable methods have been introduced to quantitate and characterize receptors for hormones and

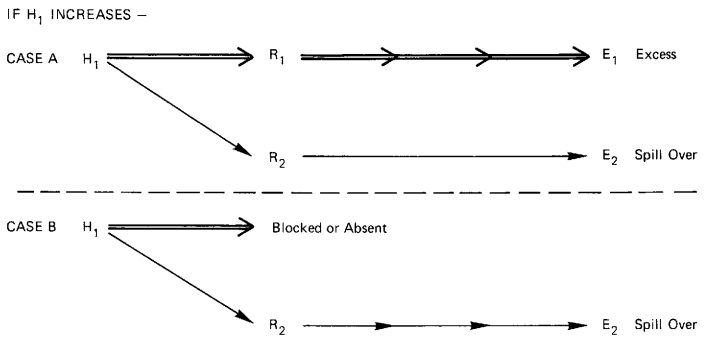

FIG. 4. Specificity spillover at the receptor. In case A, the concentration of one hormone (H_1) is increased. Through its interaction with its own receptor (R_1) it produces an excess ($\Rightarrow$) of its characteristic effects (E_1), and through its interaction with the receptors (R_2) of a related hormone, it produces effects (E_2) characteristic of the other hormone (H_2). In case B, the concentration of H_1 is increased but its own pathway of action is blocked or absent and the only biological effects (E_2) are those produced by the interaction of H_1 with R_2.

other biologically interesting ligands. Applied initially to hormone receptors on malignant cells and to androgen-resistant and insulin-resistant states, these methods have led to the identification of many disease processes where the receptor plays an important role. This includes not only endocrine-related diseases but also neurological, metabolic, infectious, and immune disorders as well.

Note. On the basis of biological and chemical data, it appears that the 40 to 50 different hormones found in a given organism each evolved from a much smaller number of primordial hormones. Presumably, for the peptide hormones the gene for the primordial hormone was duplicated as was the gene for its cell surface receptor; the new hormone–receptor pair evolved to establish a second signaling system. The affinity of each hormone for its specific receptor was high but in many cases the ligand retained some finite (albeit low) affinity for the other receptor. Thus, teleologically, greater diversity was paid for by a small loss in specificity. The weak affinity of one hormone for the receptor of a closely related hormone forms the basis for specificity spillover. The modest impairment of specificity in endocrine systems, its postulated origins, and suggested consequences may have significant counterparts in other areas of biology where diversity coexists with modest degeneracies in specificity, e.g., the large series of trypsin-like proteases that regulate multiple extracellular events such as clotting and kinin generation; neurotransmitters and related drugs; cyclase and the nucleotide-stimulated kinases; autoantibodies and prostaglandins.

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