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RECEPTORS IN CLASSICAL PHARMACOLOGY AND CELL BIOLOGY

A REPORT OF A SYMPOSIUM HELD ON THE OCCASION OF THE 25th ANNIVERSARY OF THE FIRST PUBLICATION OF *BIOCHEMICAL PHARMACOLOGY*

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Receptors have been the subject of intensive research during the past decade, and presently constitute a major facet of pharmacology and cell biology. To celebrate the 25th anniversary of *Biochemical Pharmacology*, the editors of the Journal organized a 2-day symposium on this subject. The challenge was to gather scientists from diverse fields such as pharmacology and molecular biology, in order to discuss the various biochemical realities implicit in the word "receptor". Indeed, neurotransmitter receptors are not similar to those of steroid hormones, or even less so for those of transferrin.

As the opening lecturer, P. Laduron (Beerse, Belgium) reminded us that the receptor theory originated with the work of Paul Ehrlich and John Newport Langley in the early part of the twentieth century. Langley was the first to provide a valid description of the idea of a receptor [for an historical outline, see Z. M. Bacq, *Chemical Transmission of Nerve Impulses*", Pergamon Press, Oxford (1975)] which, at that time, was called "receptive substance". In fact, this work was remarkably suited to what we have learned over the past 50 years about the molecular structure of the nicotine receptor, later described by J. O. Dolly (London, U.K.). In studying the interactions of nicotine and curare, Langley defined in 1908 a receptor as a "site of competition for agonists and antagonists: the 'receptive substance' receives the stimulus from the agonist and, by transmitting the stimulus to the cell, causes a physiological response." Hence the notion of receptor had to be coupled with that of physiological response.

To understand the mechanism of action of agonists, binding studies are undoubtedly very useful but have also led to erroneous conclusions. Numerous ligands only bind to recognition sites for chemical structures which are unrelated to a receptor site; they are simply acceptor sites. Unlike hormones, most neurotransmitters have a low affinity (micromolar range) for their receptors and are thus inappropriate ligands for binding studies.

The criteria for defining a receptor were certainly met in the case of the histamine H_2-receptor. Sir James Black (Beckenham, U.K.) explained how an operational analysis of simple pharmacological tests contributed to the differentiation between histamine H_1- and H_2-receptors. However, a physiological response such as that elicited by nerve stimulation may sometimes be the consequence of a series of events; the acid secretion produced by vagal stimulation involves not only acetylcholine release but also the secretion of gastrin and histamine. Consequently, drugs which reduce acid secretion in the stomach may act at different levels. As the histamine H_2-receptor is known to be an adenylate cyclase sensitive to histamine, relatively high concentrations of compounds are required, as is the case for many drugs which act on enzymes.

J. O. Dolly summarized 10 years of collaborative research which led to the description of the acetylcholine receptor, including the identification of the gene coding for its four subunits. Monoclonal antibodies which induce myasthenia in the mouse react with the four subunits. A detailed immunological analysis of the receptor functional domains supports the hypothesis of variability in its composition, depending upon its tissue localization.

The benzodiazepine receptor could be considered as an allosteric protein. C. Braestrup (Roskilde, Denmark) emphasized that the endogenous ligand for this receptor is still unknown. Different types of drugs contributed to the determination of the nature of the constituents involved in the control of the chloride channel opening by GABA. Benzodiazepine antagonists behave similarly to naloxone on the opiate receptor; this supports the concept that benzodiazepine may be regarded as an agonist, such as morphine. A group of compounds which belong to the β-carboline chemical class act *in vivo* both as anxiogenic and convulsant agents; Braestrup called them inverse agonists.

M. Goodhardt (Paris, France) applied receptor technology to different models used in experimental pharmacology. Among other examples, she reported that bile flow obstruction induces a decrease in the number of adrenergic α-receptors and a concomitant increase in the number of adrenergic β_2-receptors in the rat. This emphasizes the potential of pathological situations to modulate glycogenolysis regulation by changing the balance between α_1- and β_2-receptors.

A large array of neuropeptides are potential neuromediators in the CNS. P. Emson (Cambridge, U.K.) stressed that in this field, biochemical as well as pharmacological studies are still in an early phase. Even if certain neuropeptides can be studied by radioligand binding *in vitro*, such an approach is restricted by the limited knowledge of peptide phar-

macology. Neuropeptides are different from the classical neurotransmitters; behavioral, pharmacological and biochemical studies indicate that they are endowed with high-affinity properties. Researchers tend to consider these neuropeptides as neuromodulators rather than true neurotransmitters. They may regulate or modulate several effector systems in the brain, such as ion channels, cyclic nucleotide metabolism and calcium mobilization.

I. Creese (La Jolla, U.S.A.) presented a revision of his earlier hypothesis of the properties of the dopamine receptor; D_3-site now becomes the D_1-site. The D_3-site is an acceptor site for catechol derivatives and the function of D_1, the dopamine-sensitive adenylate cyclase, is still undetermined. The new hypothesis involves the assumption that [^{3}H]flupenthixol only binds to D_1- and D_2-sites, in spite of the fact that this drug is known to have a high affinity for histamine H_1 adrenergic α_1-receptors and presumably other sites.

P. B. Molinoff (Philadelphia, U.S.A.) described the β-receptors and discussed the modification in the ligand affinity when isolated membranes are compared with living cells. He commented on the potential equilibrium between intracellular and membrane-bound receptors in relation to cell desensitization for specific effectors. P. Laduron also discussed this problem. In sympathetic nerves, the presynaptic muscarinic receptors are transported by axonal flow in vesicles containing noradrenaline. Double-ligature experiments on rat sciatic nerves suggest that muscarinic receptors are recycled in the cell body after having returned from the terminals by retrograde axoplasmic transport. Such findings provide additional support for the idea that only a small number of receptors are functional; thus the analogy with the neurotransmitter itself becomes feasible.

Nerve growth factor (NGF) is required for the survival and axon growth of sympathetic and neuronal cells. E. M. Shooter (Stanford, U.S.A.) reported the existence of two NGF receptor sites on nerve cell membranes. These receptors were characterized on the basis of their different affinities for NGF; a high-affinity site might be related to the axon growth and a low-affinity site might be involved in the survival of the cells. Various experimental approaches (action of lecithins, partial enzymatic digestion, monoclonal antibodies) are currently used to define the structure of the NGF receptors in the membranes.

The insulin receptor has been studied extensively and many of its structural features at the molecular level are known. E. Van Obberghen (Nice, France) discussed in detail the insulin-mediated phosphorylation of the receptor proteins. Differences in the nature of the phosphorylated amino acids occur when intact cells or insulin receptors are used in the phosphorylation assay. The β-subunit of the insulin receptor of hepatocytes might be an insulin-activated tryosin-specific protein kinase which not only may autophosphorylate but also may phosphorylate exogenous proteins. A serine-specific protein kinase is also linked to and controlled by the insulin receptor. The existence of these two kinases again raises the interesting question of the dual role of growth factors, i.e. a metabolic and a growth control function.

Cytosolic receptors for sex hormones have been known for quite some time. Their molecular structure has not yet been clarified whereas the specificity of their binding site has been extensively studied. E. Baulieu (Bicêtre, France) has been particularly involved in the development of high-affinity antagonists of progesterone. His experimental approach, based on a basic knowledge of the biochemistry of the receptor, has led to the definition of a new, most interesting contraceptive agent, the pharmacological activity of which is presently under study in laboratory animals and man.

With respect to the biochemical mechanism involved in the control of gene expression by the steroid hormone-receptor, L. Carldstedt-Duke (Stockholm, Sweden) reported that the activated gluco ("glucocorticoid") corticoid-receptor complex binds to DNA in a specific manner. By using viral DNA as a target, it is possible to demonstrate several specific binding sites: two of them are located on the long terminal repeat sequences on the viral DNA. All of these specific recognition sites can be used by the gluco ("glucocorticoid") corticoid-receptor to control the transcription of DNA.

A review of the current status of transferrin receptor by I. S. Trowbridge (San Diego, U.S.A.) emphasized the magnitude of the impact of molecular biological techniques and monoclonal antibodies for the study of the components of the cell surface. The understanding of the structure and functions of the transferrin receptor has led to the development of interesting tools for both applied and fundamental research. Monoclonal antibodies against human and mouse transferrin receptors block the receptor function and hence the cellular growth *in vitro* and *in vivo*. Such an experimental approach should be extended to receptors of other growth factors.

Tumor promoter receptors are bound to the cell plasma membrane. As reviewed by P. Blumberg (Bethesda, U.S.A.), these receptors are well preserved during evolution from the invertebrate. However, the identification of an endogenous ligand for the tumor promoter receptor remains an intriguing problem. They are particularly found in high concentrations in the brain. Tumor promoters of distinct chemical structures compete for the same binding sites which mediate a number of biological and biochemical effects, including the specific induction of protein kinase C, a cytosolic enzyme. Diacylglycerols modify the affinity of the receptor for the promoter, but it is not clear whether this effect is linked to a direct competition or to a modification of the structure of the surrounding membrane.

The seminar was closed by a round table discussion introduced by P. Alexander (Southampton, U.K.) on the biological importance of growth factor interaction with its receptor in the development of malignant cells. This subject is of particular interest because of the recent discovery that one oncogene is related to one growth factor gene.

A detailed report of the symposium will appear in a forthcoming issue of *Biochemical Pharmacology*.