Receptor Dysfunctions in Human Disease

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Summary. The characterization of binding parameters of hormones and drugs to specific receptors at various human cell types have introduced an interesting approach for the evaluation of pathogenic mechanisms involved in endocrine and metabolic disorders. The dysregulation of cellular receptors in those disease include changes in receptor number, changes in binding affinity and production of antibodies against receptor molecules. It can be concluded from these observations that altered receptor physiology may be of important value for abnormalities in cellular recognition and control mechanisms which can be observed in neoplastic, inflammatory, immune and developmental diseases.

Key words: Specific binding mechanisms – Cellular receptors – Hormone action – Hormone resistance – Receptor dysregulations

Introduction

How can intracellular transfer of information be accomplished following a specific chemical signal leading to a particular biological response? To answer this question basic research has accumulated many informations regarding interactions of specific cellular receptors with their corresponding effector molecules, i.e. hormones, neurotransmitters, drugs or even microbial products. Hormone receptors can be divided into three classes, depending on their localisation in their different target cells: firstly, steroid hormone receptors are localised in the intracellular compartment associated with the nucleus of certain target cells [7, 19, 20, 26, 64]. Secondly, thyroid hormones have been found attached to chromatin of target cells [8, 9, 54], and thirdly, receptors for polypeptide hormones, catecholamines and releasing factors have been demonstrated on the external surface of plasma membranes of various target cells [18, 23, 40].

Though the recognition of effector molecules by the target tissue is thought to occur via specific binding of the substances to cellular receptors, the detailed molecular mechanisms by which binding is achieved are mainly unknown. However, there are various clinical situations which can be related to changes in the biological effects of hormones as the result of abnormal hormone binding characteristics to the target cells. On the other hand, receptor binding studies...
with certain ligands may not necessarily explain all pathogenic mechanisms of hormone related diseases but they provide an interesting tool for analysis of receptor abnormalities in human disease.

The Cellular Receptor

Cellular receptors confer specificity to the hormone system and are designed to recognize the biologically active hormone molecule. Membrane receptors which are located at the outer cell membrane are usually glycoproteins, composed of subunits of approx. 10^5 daltons and are closely associated with membrane lipids. The number of receptors per cell is limited being maximally thousands per cell, indicating that the binding of a certain ligand is saturable. Cellular receptors can be demonstrated on intact cells (e.g. circulating leucocytes, lymphocytes, and tumor cells), they can be enzymatically isolated from the liver and the fat, they are present on broken cells (crude homogenates or purified plasma membranes) and can be solubilized spontaneously (e.g. from lymphocytes) with detergents. The way by which the bound hormone affects cellular behaviour has been studied by Cuatrecasas [23, 46]. These observations indicate that the hormone-receptor-complex diffuses laterally along the membrane surface of the target cell till it couples and activates a separate effector molecule.

Hormone Receptor Interaction

For analysis of hormone binding to receptor molecules, the binding process has to occur at equilibrium which is usually achieved after one to two hours, but sometimes after 24 to 36 h of incubation. The binding of ligands to cellular receptors is usually reversible and is a temperature- and pH-dependent process (Table 1).

The interaction between a hormone (H) and the receptor (R) is thought to form a hormone-receptor-complex (HR). The rate at which (H) and (R) combine to form (HR) is a forward reaction, giving an association constant (k1):

\[ H + R \overset{k_1}{\underset{k_2}{\rightleftharpoons}} HR. \]

Hormone binding is usually reversible, therefore the dissociation of the hormone-receptor-complex can be dissociated in a backward reaction leading to the dissociation constant (k2):

\[ [HR] \overset{k_2}{\underset{k_1}{\rightleftharpoons}} [H] + [R]. \]

Thus, at equilibrium binding, the rates of back- and forward reaction are equal:

\[ k_1 = k_2. \]

Considering that half the receptors are saturated by the hormone, the concentration of sites and that of the hormone-binding-complex are equal and can be cancelled. Under these conditions the dissociation constant (KD) equals the free hormone concentration

\[ [H] \frac{[R]}{[HR]} = \frac{k_1}{k_2} = K_D \]

necessary to half maximal saturate receptors:

\[ [H] = K_D \]

The KD values are an important measure for definition of affinity of the hormone to its receptors, i.e. the higher the KD value, the lower is the affinity of hormone binding. The affinity of a hormone to its corresponding receptors is accomplished by noncovalent binding and enables the receptor to distinguish a particular hormonal signal from others.

Hormone receptor assays contain control measurements to distinguish high affinity, saturable specific binding from low affinity, non-specific binding to other cell proteins being invariably present. This is done by parallel measurements of bound ligand in the presence of radiolabeled ligand (e.g. 125I, 3H) plus a hundredfold excess of unlabeled ligand. The unlabeled ligand is assumed to saturate all specific

<table>
<thead>
<tr>
<th>Table 1. Systems for measuring and localizing receptors</th>
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<tbody>
<tr>
<td>Receptor Assay:</td>
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<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Closely related to biological; major structural</td>
</tr>
<tr>
<td>similarities are ignored if not related to bioeffect;</td>
</tr>
<tr>
<td>great structural differences ignored if bioactive</td>
</tr>
<tr>
<td>regions are intact</td>
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<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Limited by the affinity of the naturally occurring</td>
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<tr>
<td>receptor; can be increased a few fold by sage selection</td>
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<tr>
<td>of incubation conditions</td>
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<tr>
<td>binding reagents variability</td>
</tr>
<tr>
<td>Ubiquitous, uniform, easy to obtain</td>
</tr>
<tr>
<td>Binding reagents variability</td>
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<tr>
<td>Time to reach equilibrium</td>
</tr>
<tr>
<td>Minutes/Hours</td>
</tr>
<tr>
<td>Whole plasma</td>
</tr>
<tr>
<td>In some cases may interfere; needs more study. Often</td>
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<tr>
<td>hormone separated from bulk of plasma by gel filtration</td>
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<td>or chromatography on immunoadsorbent column</td>
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