MATHEMATICS OF HORMONE-RECEPTOR INTERACTION

I. BASIC PRINCIPLES

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The basic principles underlying simple bimolecular reactions
are reviewed. Alternative methods for estimation of rate constants
and affinity constants are discussed. The need for weighting,
itration, and testing of alternative models is emphasized. Common
problems and errors are discussed.

GENERAL INTRODUCTION

The interaction of hormones with their receptors in target
tissues may be analyzed by use of several mathematical models pre-
viously developed for other ligand-binding systems. These models
provide a precise, quantitative description of the system, permit
computer-simulation studies, and least-squares or maximum-likeli-
hood estimates of parameters, as an adjunct to experimentation, and
provide an objective quantitative basis for tests of the "goodness-
of-fit" of alternative biochemical mechanisms.

The study of hormone-receptor interactions is still in its in-
fancy. Only a few receptors have been isolated or studied in puri-
fied form. Until both the hormone(s) and receptor(s) are available
in homogenous form, it will be nearly impossible to delineate the
intricacies of the reaction mechanisms, and obtain realistic mathem-
atical and physical-chemical models.

In contrast, the theories for enzyme-substrate-inhibitor systems,
for cooperative ligand binding (e.g., of O2 to hemoglobin), and
for drug-receptor binding have reached maturity, and have been des-
cribed extensively in the biochemical-biophysical (1-19), pharmaco-
logical (20-24), statistical (25-27), and radioimmunoassay (28-41)
Part I of this article will deal primarily with the "simple" models for bimolecular interaction. Emphasis is placed on the statistical problems encountered in the estimation of reaction rate constants and affinity constants. Part II will consider the most elementary model of "cooperative" binding (the sequential or consecutive reaction model, with only 2 sites), as applied to hormone-receptor and radio-ligand assay systems. Methods for simulation of dose response curves, both prior to and at equilibrium, are provided. Part III will consider the relationship between "binding" of the hormone and the "response" of the target cell or target tissue. A simple "QUANTAL" model is proposed, to account for dissociation between binding, intermediate response (e.g., cAMP) and ultimate response (e.g., steroid biosynthesis and/or secretion). This theory regards the cell, rather than the binding site, as the quantal unit for response, provides an explanation for the vast excess of spare receptors, and may serve to unify the "occupancy" and "rate" theories of drug/hormone action.

PART I. REVIEW OF BASIC PRINCIPLES

The most elementary description of hormone-receptor interaction is given by reaction scheme I:

\[
\begin{align*}
\text{P} + \text{Q} & \xrightleftharpoons[k_1']{k_1} \text{PO} \\
\end{align*}
\]

This model assumes homogeneity of both the hormone (P) and receptor (Q). These two species react reversibly according to the first order mass-action law, forming the hormone-receptor complex (PO). The differential equations describing this system, viz.:

\[
\frac{d[pO]}{dt} = k_1(p - [pO])(q - [pO]) - k_1' [pO]
\]

are second-order, and we regard this as second order chemical kinetics. An analytical solution to this equation is available (37,39), (Appendix, A.1).

If the dissociation rate constant, k' is zero, then we have a second-order irreversible reaction, and the form of the analytical solution changes, depending on whether one has perfect identity (p = q) or non-identity of the molar concentrations of hormone and receptor (Appendix, A.2, A.3).

The first step in analysis of a hormone-receptor system is to perform a "kinetic" or time study, to follow the association of P and Q, and/or the dissociation of PQ. This is necessary, even if one only wishes to obtain the "equilibrium constant of association",