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International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. IX. Recommendations on Terms and Symbols in Quantitative Pharmacology

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I. Introduction

The literature of pharmacology presents many inconsistencies in the use of nomenclature and symbols. These are particularly common in operational studies in which receptors are characterized by quantitative measurements of receptor-mediated function and of ligand binding. The problem is compounded by the fact that sometimes a given term is used in quite different senses. For these reasons, it would, we believe, be helpful to adhere to (so far as is practicable and reasonable) a common terminology, set of definitions, and symbol usage. These issues have been addressed in most other biological and physical sciences, and the approach taken by the International Union of Pure and Applied Chemistry (IUPAC) seems particularly relevant to us (see, for example, Mills et al. 1993)

The recommendations that follow have been prepared as one of the objectives of a Technical Subcommittee set up by the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification. The authors are most grateful to the other subcommittee members and to a panel of

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distinguished pharmacologists who served as corresponding members. All provided invaluable comments and suggestions for the improvement of successive drafts. These consultations notwithstanding, the recommendations that follow are to be regarded as provisional in nature. Their aim is to aid communication and ease of comprehension without being rigidly prescriptive, and they will certainly require periodic revision and updating as new ideas and information arise. With this in mind, the Technical Subcommittee welcomes comments and suggestions. All correspondence should be addressed to the subcommittee chairman, P. P. A. Humphrey (see footnote).

It should be added that variations from the suggested notation and usage may well be desirable under particular circumstances. For example, subscripts can be omitted where no ambiguity would result, or additional subscripts or superscripts may be added in the interests of clarity. The only essential is that the new terms are clearly defined.

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II. Recommendations

As a general principle, these follow the recommendations of the International Union of Pure and Applied Chemistry (Mills et al., 1993), albeit with variations and extensions prompted by the requirements of pharmacology.

A. The Expression of Amount of Drug: Concentration and Dose

1. Concentration. It is recommended that the molar concentration of substance *X* be denoted by either [X] or c_X, with the former preferred. Decimal multipliers should be indicated by the use of either Le Système International d'Unités (International System of Units) prefixes (e.g., μM, nM) or by powers of ten (e.g., 3×10^{-8} M), with the former preferred.

2. Dose. In some circumstances (e.g., in therapeutics and clinical pharmacology, in in vivo experiments, and when tissues are perfused in vitro and exposed to a bolus application of drug), absolute drug concentrations are uncertain, and it becomes more appropriate to specify the quantity of drug administered. This may be done in terms of either mass or molar quantity. Units and routes of administration should be specified. In the case of in vivo experiments with animals, the quantity of drug is to be expressed per unit of animal mass (e.g., mol/kg, mg/kg). In therapeutics, mg/kg will normally be appropriate. Negative indices should be used where confusion could otherwise arise (e.g., mg min^{-1} kg^{-1}).

B. General Terms Used to Describe Drug Action

Table 1.

C. Empirical Measures of Drug Action

1. General measures. Table 2.
2. Agonists. Table 3.
3. Antagonists. Table 4.

D. Terms and Procedures Used in the Analysis of Drug Action

1. The quantification of ligand-receptor interactions. Table 5.
2. Action of agonists. Table 6.
3. Action of antagonists. Table 7.

TABLE 1

General terms used to describe drug action

Term	Suggested usage	Notes
Agonist	A ligand that binds to receptors and thereby alters the proportion of them that are in an active form, resulting in a biological response. Conventional agonists increase this proportion, whereas *inverse agonists* (which see) reduce it.	Agonists may act by combining either with the same site(s) as the endogenous agonist or, less commonly, with a different region of the receptor macromolecule. Agonists in the second category are sometimes referred to as *allosteric agonists or activators*. Some agonists (e.g., glutamate) may only be effective in the presence of another ligand (e.g., glycine in the case of glutamate) that binds to a different site on the receptor macromolecule. Under these circumstances, glutamate is referred to as the *primary agonist* and glycine as a *co-agonist*.
Antagonist	A drug that reduces the action of another drug, generally an agonist. Many act at the same receptor macromolecule as the agonist. Antagonists of this kind may be *surmountable* or *insurmountable*, depending on the experimental conditions (see table 7). Antagonism may also result from combination with the substance being antagonized (*chemical antagonism*), or the production of an opposite effect through a different receptor (*functional antagonism*) or as a consequence of competition for the binding site of an intermediate that links receptor activation to the effect observed (*indirect antagonism*). The term *functional antagonism* is also used to describe a less well-defined category in which the antagonist interferes with other events that follow receptor activation.	The term *physiological antagonism* has also been used to describe the action of a substance that exerts an opposite effect to an agonist.
Modulator	A ligand that increases or decreases the action of an agonist by combining with a distinct (allosteric) site on the receptor macromolecule.	
Receptor	Cellular macromolecules that are concerned directly and specifically in chemical signalling between and within cells. Combination of a hormone, neurotransmitter, drug or intracellular messenger with its receptor(s) initiates a change in cell function. The regions of the receptor macromolecule to which endogenous agonists bind are referred to collectively as the *recognition site(s)* of the receptor.	

TABLE 2

Empirical measures of drug action: general

Term	Suggested usage	Notes
The relationship between concentration and effect: Hill equation.	In the following, drug action is expressed in terms of the effect, E, produced when an agent, A, is applied at a concentration [A]. The relationship between E and [A] can often be described empirically by the Hill equation which has the form: $$\frac{E}{E_{max}} = \frac{[A]^{n_H}}{[A]_{50}^{n_H} + [A]^{n_H}}$$ where E_{max} is the maximal action of A, n_H is the Hill coefficient and $[A]_{50}$ is the concentration that produces an effect that is 50% of E_{max}.	$[A]_{50}$ in the Hill equation is sometimes denoted by K, and E_{max} by α. The choice between $[A]_{50}$ and K will depend on the directness of the measurement. The former is appropriate if an indirect action, such as the contraction of an intact smooth muscle preparation, is observed. However, in a ligand binding experiment, K would be preferable, although whether the value of K corresponds to a single dissociation equilibrium constant (even if n_H is unity) will depend on the circumstances (see Appendix, III.A.). The *Hill equation* and the *logistic equation* are closely related but not identical (see Appendix, III.C.).
Potency	An expression of the activity of a drug, either in terms of the concentration or amount needed to produce a defined effect, or, less acceptably, with regard to the maximal effect attainable. An imprecise term that should always be further defined (see EC_{50}, IC_{50}, *Maximal agonist effect*, etc.).	

TABLE 3
Empirical measures of drug action: agonists

Term	Suggested usage	Notes
EC_{50} or $[A]_{50}$	The molar concentration of an agonist that produces 50% of the maximal possible effect of that agonist. Other percentage values (EC_{20}, EC_{40}, etc.) can be specified. The action of the agonist may be stimulatory or inhibitory.	The mass concentration (g/l) to be used if the molecular weight of the test substance is unknown. It may sometimes be preferable to express the activity of a drug in terms of the concentration that causes a specified change in a baseline measurement (e.g., a 20-mm Hg change in perfusion pressure; a 30% increase in a muscle twitch). If the EC_X (or $[A]_X$) terminology is to be used in this context, the appropriate units must be included (e.g., EC_{20mm} or $[A]_{30\%}$) to avoid confusion with EC_{20} or $[A]_{30}$ as here defined. Under some circumstances, it may become appropriate to use these terms in a more general sense. For example, the application of an antagonist to an intact tissue can reduce the action of an endogenous agonist that exerts an inhibitory effect. Thus, an α_2-adrenoceptor antagonist such as yohimbine will block inhibitory α_2-autoreceptors on noradrenergic nerve endings. The outcome will be a rise in noradrenaline release. If this release is measured, it will be increased in a graded fashion by the antagonist. Under such circumstances, when the agonist concentration is unknown, this action of the antagonist can be characterized in terms of an EC_{50} or $[A]_{50}$. If, however, the concentration of agonist is known, then the measures of antagonist action considered in the next table (table 4) should be used.
ED_{50}	*Either* the dose of a drug that produces, on average, a specified all-or-none response in 50% of a test population *or, if the response is graded,* the dose that produces 50% of the maximal response to that drug	Units (e.g., mg/kg, mmol/kg or mg/l, mmol/l when a tissue is perfused) to be given. Applicable to in vivo measurements and to those in vitro experiments (e.g., with a perfused tissue) in which absolute concentration is uncertain. Otherwise use EC_{50}. In some circumstances, the maximum response will be unknown. This will often be so in clinical pharmacology, for considerations of safety. The effectiveness of a drug may then be best expressed in terms of the dose that causes, for example, a certain change in blood pressure or heart rate. If the ED terminology is to be used for such measurements, the appropriate units must be included (e.g., ED_{20mm}) to avoid confusion with the usage recommended in the left column.
pEC_{50} or $p[A]_{50}$	The negative logarithm to base 10 of the EC_{50} of an agonist.	The term pD_2 has also been used, particularly in the earlier literature.
Maximal agonist effect, α	The maximal effect that an agonist, whether conventional or inverse, can elicit in a given tissue under particular experimental conditions, expressed as a fraction of that produced by a full agonist acting through the same receptors under the same conditions.	Also referred to as *intrinsic activity*, although the term *maximal agonist effect* is preferred. See also *Efficacy* (table 6).
Equi-effective molar concentration ratio, EMR	The ratio of the molar concentrations of test and reference substances that produce the same biological effect (whether activation or inhibition).	Should only be specified if the log concentration-effect curves for the substances being compared are parallel.
Equi-effective dose ratio, EDR	As above, but used when doses rather than concentrations are compared, as in in vivo work.	

TABLE 4

Empirical measures of drug action: antagonists

Term	Suggested usage	Notes
Concentration ratio, *r*	The ratio of the concentration of an agonist that produces a specified response (often but not necessarily 50% of the maximal response to that agonist in an assay) in the presence of an antagonist, to the agonist concentration that produces the same response in the absence of antagonist.	The traditional term *dose ratio* is considered less appropriate.
IC_{50}	*Either* the molar concentration of an antagonist that reduces a specified response to 50% of its former value (see also EC_{50}) *or* the molar concentration of an agent (agonist or antagonist) that causes a 50% reduction in the specific binding of a radioligand.	If the response being reduced is elicited by an applied agonist, its concentration should be stated. The concentration of the radioligand should be stated together with its dissociation equilibrium constant, if known.
pA_2	The negative logarithm to base 10 of the molar concentration of an antagonist that makes it necessary to double the concentration of agonist needed to elicit the original submaximal response (Schild, 1947).	An empirical measure of the activity (in concentration terms) of an antagonist that is not dependent on how the antagonist acts. For reversible competitive antagonists, pA_2 can be determined by measuring the value of the concentration ratio *r* at several antagonist concentrations, allowing an estimate of the antagonist concentration at which *r* would be 2. This is commonly done by graphical extrapolation or interpolation (without constraining the slope of the line). Note that pA_2 and pK_B coincide only under specific circumstances (see *Schild equation*, *Schild plot* and table 7).

TABLE 5

Terms and procedures used in the analysis of drug action: the quantification of ligand-receptor interactions

Term	Suggested usage	Notes
'Concentration' of receptors	[R] for nominal concentration of ligand-free receptors; $[R]_T$ or $[R]_{tot}$ for total receptors.	
Number of receptors, N	The total number of receptors, expressed in terms of unit area of membrane, or per cell, or per unit mass of protein.	Proportional to the quantity B_{max} (the maximal specific binding of a ligand, often expressed in units of mol ligand/mg protein, or /cell) measured in radioligand binding studies, in the absence of complications. The relationship between B_{max} and N is influenced by the number of ligand binding sites possessed by each receptor. For ligand-gated ion channels, this is generally greater than one. Also referred to as *receptor density*.
Proportion of receptors in specified states	p_R for proportion (fraction) of receptors or binding sites free of ligand. p_{LR} for the proportion of receptors or binding sites occupied by the ligand L. If a distinction is made between inactive and active states of the receptor, then p_{LR} refers to the former. p_{LR^*} for the proportion of receptors in which L occupies its binding site(s) and which are in an active state.	Other subscripts and qualifiers may be appropriate, depending on the scheme under consideration.
Rate constants for the binding of a ligand	k_{+1} for the association (forward) rate constant, and k_{-1} for the dissociation (backward) rate constant, in the reaction $L + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} LR$ Here L represents a ligand and R the unoccupied binding site	Units to be specified ($M^{-1}\,s^{-1}$ for k_{+1}, s^{-1} for k_{-1} in the scheme illustrated). Lower case symbols to be used to denote rate constants (cf., upper case for equilibrium constants). Where there are several ligands, alphabetical subscripts can be added: e.g., k_{+1A}, k_{-1B} For more complicated schemes involving several reactions, subscripts 2, 3,. . . . can be used: e.g., $A + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} AR \underset{k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} AR^*$

Dissociation equilibrium constant for ligand-receptor interactions

K, numerically equal to k_{-1}/k_{+1}, and with the dimension M, for the scheme

$$L + R \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} LR$$

For clarity, subscripts (upper case alphabetical, e.g., K_B, K_L, numerical, e.g., K_2, or a combination of the two, e.g., K_{2L}) can be added to identify the particular ligands and equilibria under consideration, especially when dealing with more complicated schemes involving several steps such as binding followed by isomerization:

$$A + R \underset{}{\overset{K_{1A}}{\rightleftharpoons}} AR \overset{K_{2A}}{\rightleftharpoons} AR^*$$

$$L + R \underset{}{\overset{K_{1L}}{\rightleftharpoons}} LR \overset{K_{2L}}{\rightleftharpoons} LR^*$$

The word order in *dissociation equilibrium constant* is suggested for consistency with *dissociation rate constant* and *association rate constant*.

The reciprocal (the *association equilibrium constant* or *affinity constant*, M^{-1}) of the dissociation equilibrium constant can also be used, although this is not preferred.

If a subscripted symbol is required when presenting the results of experiments to measure dissociation equilibrium constants (e.g., by means of ligand binding), K_d should be used in preference to K_D.

See also Appendix, III.A.

Hill-Langmuir equation

$$p_{LR} = \frac{[L]}{K_L + [L]}$$

in which p_{LR} is the fraction (proportion) of binding sites occupied by a ligand L at equilibrium. It is assumed that the interaction between L and the sites obeys the law of mass action and can be described by the simple scheme

$$L + R \underset{}{\overset{K_L}{\rightleftharpoons}} LR$$

in which K_L is the dissociation equilibrium constant.

Described as the Langmuir adsorption isotherm in physical chemistry.

Although K rather than K_L could have been written for this simple scheme, a subscript is commonly added (see *Dissociation equilibrium constant*, in this table).

More complicated expressions may hold, especially if L is an agonist (see Appendix, III.A.).

TABLE 6

Terms and procedures used in the analysis of drug action: agonists

Term	Suggested usage	Notes
Desensitization, fade, tachyphylaxis	Overlapping terms that refer to a spontaneous decline in the response to a continuous application of agonist, or to repeated applications or doses. The following usages are suggested: *Fade*—the waning of a response in the continued presence of agonist. *Tachyphylaxis*—a decline in the response to repeated applications or doses of agonist. No mechanism is implied by either term. It is recommended that *desensitization* be used when the fade or tachyphylaxis is considered to involve the receptor itself, or to be a direct consequence of receptor activation.	
Efficacy, e	The concept and numerical term introduced by Stephenson (1956) to express the degree to which different agonists produce varying responses, even when occupying the same proportion of receptors. (See also *Maximal agonist effect*, table 3)	In Stephenson's formulation (1956), combination of an agonist with its receptors is considered to result in a signal or "stimulus" S, which is equated to the product of the efficacy of the agonist, A, and the proportion of receptors occupied: $S_A = e_A p_{AR}$ When the response of a tissue is half-maximal, S is assigned the value unity. Hence, a partial agonist that when occupying all the receptors produces a maximal response that is half that to a full agonist (under the same experimental conditions), has an efficacy of unity. Efficacy is both agonist- and tissue-dependent. The expression *intrinsic efficacy*, ϵ, was introduced by Furchgott (1966) to denote the notional efficacy associated with a single receptor: $e = \epsilon[R]_T$ in which $[R]_T$ indicates the total concentration of receptors. This term is now also used in a wider sense (see paragraph after next). Black and Leff (1983) provided another description of differences in the ability of agonists to produce a maximal effect. They defined the term τ (*tau*) as $[R]_T/K_E$, in which K_E is the midpoint parameter of an explicit function relating receptor occupancy to the response of a tissue. Recent advances in the understanding of receptor function have identified the importance of distinguishing between the *occupation* of a receptor by an agonist and the *activation* of that receptor. This distinction was not considered in the earlier work. More detailed models of receptor action are therefore required, and these provide a better framework for expressing, and explaining, differences in the ability of agonists to activate receptors. The term *intrinsic efficacy* is now often used when discussing the agonist, rather than the tissue-dependent component of efficacy in such schemes (e.g., the isomerization model of del Castillo and Katz (1957), also Colquhoun (1987); the ternary model of DeLean et al. (1978), also Samama et al. (1993)). However, Stephenson's *efficacy*, and Black and Leff's (1983) τ, can still serve as useful comparative measures of the activity of agonists on intact tissues.

Full agonist	When a tissue has spare receptors (which see), several agonists may be able to elicit the same maximal response, albeit at different receptor occupancies. They are said to be full agonists in that experimental situation. A full agonist in one tissue may be a partial agonist in another.	
Inverse agonist	A ligand which by binding to receptors reduces the fraction of them in an active conformation (see also agonist, table 1). This can occur if some of the receptors are in the active form (R*), even in the absence of a conventional agonist: $\underset{\text{(inactive)}}{R} \rightleftharpoons \underset{\text{(active)}}{R^*}$ If the ligand, L, combines preferentially with inactive receptors, it will reduce the fraction in the active state: $\underset{\text{(inactive)}}{LR} \rightleftharpoons \underset{\text{(inactive)}}{L + R} \rightleftharpoons \underset{\text{(active)}}{R^*}$	An inverse agonist may combine either with the same site as a conventional agonist, under which circumstance it is sometimes referred to as a *negative antagonist* (because it can compete with another agonist), or with a different site on the receptor macromolecule (see table 1).
Intrinsic efficacy	See *Efficacy* (above, in this table).	
Partial agonist	An agonist that in a given tissue, under specified conditions, cannot elicit as large an effect (even when applied at high concentration, so that all the receptors should be occupied) as can a full agonist acting through the same receptors. (See also *Full agonist* and *Efficacy*—above, in this table—and *Maximal agonist effect*, table 3.)	Recent advances make it clear that the inability of a particular agonist to produce a maximal response can have several explanations. Perhaps the most important is that not enough of the receptors occupied by the agonist convert to an active form, and the term *partial agonist* is now sometimes applied to this situation alone. The distinction between such usages can be illustrated by the action of decamethonium at the neuromuscular junction. Decamethonium cannot match the conductance increase caused by acetylcholine. However, this is not because decamethonium is less able to cause the receptors to isomerize to an active form: rather, the smaller maximal response is largely a consequence of the greater tendency of decamethonium to block the ion channel that is intrinsic to the nicotinic receptor. Hence, decamethonium would not be regarded as a partial agonist in the particular sense defined above.
Spare receptors, receptor reserve	In some tissues, agonists of high efficacy can produce a maximal effect, even when a small fraction of the receptors are occupied. It is therefore possible to inactivate some of the receptors (e.g., by applying an irreversible competitive antagonist) without reducing the maximal response (although the curve relating the effect to the concentration of agonist will be shifted to the right). The tissue is said to possess *spare receptors*, and for a given level of response, there is a large *receptor reserve* for the action of that agonist.	Receptor reserve is both tissue- and agonist-dependent. An agent that is a partial agonist in one tissue may act as a full agonist in a second tissue with a greater receptor reserve for full agonists.

TABLE 7

Terms and procedures used in the analysis of drug action: antagonists

Term	Suggested usage	Notes
Competitive antagonism	In competitive antagonism, the binding of agonist and antagonist is mutually exclusive. This may be because the agonist and antagonist compete for the same binding site or combine with adjacent sites that overlap. A third possibility is that different sites are involved but that they influence the receptor macromolecule in such a way that agonist and antagonist molecules cannot be bound at the same time. If the agonist and antagonist form only short-lasting combinations with the receptor, so that equilibrium between agonist, antagonist and receptors is reached during the presence of the agonist, the antagonism will be surmountable over a wide range of concentrations (*reversible competitive antagonism*). In contrast, some antagonists, when in close enough proximity to their binding site, may form a stable covalent bond with it (*irreversible competitive antagonism*), and the antagonism becomes *insurmountable* when no spare receptors remain. More generally, the extent to which the action of a competitive antagonist can be overcome by increasing the concentration of agonist is determined by the relative concentrations of the two agents, by the association and dissociation rate constants for their binding, and by the duration of the exposure to each. The action of a competitive antagonist can therefore be surmountable under one set of experimental conditions and insurmountable under another.	The term *unsurmountable* rather than *insurmountable* was used in the early literature.
Noncompetitive antagonism	Agonist and antagonist can be bound simultaneously: antagonist binding reduces or prevents the action of the agonist.	This usage covers situations as diverse as channel block of the nicotinic receptor and inhibition by adrenoceptor antagonists of the response to tyramine (see *indirect antagonism*, table 1).
Gaddum equation	$$p_{AR} = \frac{[A]}{K_A\left(1 + \frac{[B]}{K_B}\right) + [A]}$$	Equating equal occupancies by an agonist first in the absence and then in the presence of a reversible competitive antagonist leads to the *Schild equation* (which see), and the terms *Schild equation* and *Gaddum equation* have sometimes been regarded as interchangeable.

The relationship (Gaddum, 1937, 1943) that replaces the Hill-Langmuir equation (which see) when two ligands, A and B, are in equilibrium with a common binding site. P_{AR} is the proportion of the binding sites occupied by A.

The Schild equation

$$r - 1 = \frac{[B]}{K_B}$$

The relationship (Schild, 1949) which would be expected to hold between the concentration ratio, r, and the concentration of a reversible competitive antagonist, B. K_B is the dissociation equilibrium constant for the combination of B with the receptor.

See also *Gaddum equation* (item above), *Schild plot* (item below), and Appendix, III.B.

The Schild plot

A graph of log $(r - 1)$ against log antagonist concentration, where r is the concentration ratio (which see). This should yield a straight line of unit slope if the Schild equation is obeyed (Arunlakshana and Schild, 1959).

The linearity and slope provide information about the nature of the antagonism (see Appendix, III.B.).

Calculation of K_B for a reversible competitive antagonist. If the line is adequately defined experimentally and is straight (but has a slope which is not unity although not differing significantly from it), it is appropriate to constrain the slope to unity. The intercept on the log concentration axis then provides an estimate not of pA_2 (given by the intercept of the unconstrained line) but of pK_B, the negative logarithm of K_B, the dissociation equilibrium constant for the combination of B with the binding site. pA_2 (which see) and pK_B coincide only if the slope is exactly unity, and there are no complicating factors (see also Appendix, III.B.).

III. Appendix

A. Microscopic and Macroscopic Equilibrium Constants

Microscopic and *macroscopic* equilibrium constants should be distinguished when describing complex equilibria, as occur with all agonists. The latter refers to the overall equilibrium (i.e., the value that would be obtained in a ligand binding experiment). For the scheme

$$A + R \underset{}{\overset{K_1}{\rightleftharpoons}} AR \overset{K_2}{\rightleftharpoons} AR^*$$

the *macroscopic dissociation equilibrium constant* is given by

$$K_{eff} = \frac{K_1 K_2}{1 + K_2}$$

Here, K_1 and K_2 are the *microscopic equilibrium constants*. Note that on this scheme, Furchgott's (1966) irreversible antagonist method for determining the dissociation equilibrium constant for an agonist would provide an estimate of K_{eff} rather than K_1.

This distinction is also important when considering those receptors (e.g., ligand-gated ion channels) that have more than one binding site for the agonist.

B. Schild Equation and Plot—Further Detail

The Schild equation is based on the assumptions that (*a*) agonist and antagonist combine with the receptor macromolecule in a freely reversible but mutually exclusive manner, (*b*) equilibrium has been reached and that the law of mass action can be applied, (*c*) a particular level of response is associated with a unique degree of occupancy or activation of the receptors by the agonist, (*d*) the response observed is mediated by a uniform population of receptors, and (*e*) the antagonist has no other relevant actions, e.g., on the relationship between receptor and response.

For an antagonist to be classified as *reversible and competitive* on the basis of experiments in which a biological response is measured, the following criteria must hold:

a) in the presence of the antagonist, the log agonist concentration-effect curve should be shifted to the right in a parallel fashion.

b) the relationship between the extent of the shift (as measured by the *concentration ratio*) and the concentration of the antagonist should follow the Schild equation over as wide a range of antagonist concentrations as practicable. Usually, the data are presented in the form of the Schild plot, and adherence to the Schild equation is judged by the finding of a linear plot with unit slope. Non-linearity and slopes other than unity can result from many causes. For example, a slope greater than 1 may reflect incomplete equilibration with the antagonist or depletion of a potent antagonist from the medium, as a consequence either of binding to receptors or other structures, or of partitioning into lipid. A slope that is significantly less than 1 may indicate removal of agonist by a saturable uptake process, or it may arise because the agonist is acting at more than one receptor (the Schild plot may then be non-linear). See Kenakin (1993) for a detailed account.

The finding that the Schild equation is obeyed over a wide range of concentrations does not prove that the agonist and antagonist act at the same site. All that may be concluded is that the results are in keeping with the hypothesis of mutually exclusive binding, which may of course result from competition for the same site but can also arise in other ways.

C. The Relationship Between the Hill and Logistic Equations

The logistic function is defined by the equation

$$y = \frac{1}{1 + e^{-(a+bx)}}$$

where a and b are constants. If a is redefined as $-\log_e(K^b)$, and x as $\log_e z$, then

$$y = \frac{z^b}{K^b + z^b}$$

which has the same form as the Hill equation.

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