# 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

[^0]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
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 $c_{\mathrm{x}}$, with the former preferred. Decimal multipliers should be indicated by the use of either Le Systeme International d'Unités (International System of Units) prefixes (e.g., $\mu \mathrm{M}, \mathrm{nM}$ ) or by powers of ten (e.g., $3 \times 10^{-8} \mathrm{~m}$ ), 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., $\mathrm{mol} / \mathrm{kg}, \mathrm{mg} /$ kg ). In therapeutics, $\mathrm{mg} / \mathrm{kg}$ will normally be appropriate. Negative indices should be used where confusion could otherwise arise (e.g., $\mathrm{mg} \mathrm{min}^{-1} \mathrm{~kg}^{-1}$ ).

## 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
4. The quantification of ligand-receptor interactions. Table 5.
5. Action of agonists. Table 6.
6. 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. <br> 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.

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 3
Empirical measures of drug action: agonists

| Ter | Suggested usage | Notes |
| :---: | :---: | :---: |
| $\mathrm{EC}_{50}$ or $[\mathrm{A}]_{50}$ | The molar concentration of an agonist that produces $50 \%$ of the maximal possible effect of that agonist. Other percentage values ( $\mathrm{EC}_{20}, \mathrm{EC}_{40}$, etc.) can be specified. The action of the agonist may be stimulatory or inhibitory. | The mass concentration (g/) to be used if the molecular weight of the test substance is unknown. <br> 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 $\mathrm{EC}_{\mathbf{x}}$ (or $[\mathrm{A}]_{\mathbf{x}}$ ) terminology is to be used in this context, the appropriate units must be included (e.g., $\mathrm{EC}_{20 \mathrm{~mm}}$ or $[\mathrm{A}]_{30 \%}$ ) to avoid confusion with $\mathrm{EC}_{20}$ or $[\mathrm{A}]_{30}$ as here defined. <br> 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 $\alpha_{2}$-adrenoceptor antagonist such as yohimbine will block inhibitory $\alpha_{2}$ 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 $\mathrm{EC}_{50}$ or $[\mathrm{A}]_{50}$. If, however, the concentration of agonist is known, then the measures of antagonist action |


| $E D_{50}$ | Either <br> 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., $\mathrm{mg} / \mathrm{kg}, \mathrm{mmol} / \mathrm{kg}$ or $\mathrm{mg} / \mathrm{mmol} / /$ when a tissue is perfused) to be given. <br> 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 $\mathrm{EC}_{50}$. <br> 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., $\mathrm{ED}_{20 \mathrm{~mm}}$ ) to avoid confusion with the usage recommended in the left column. |
| :---: | :---: | :---: |
| $\mathrm{pEC}_{50}$ or $\mathrm{p}[\mathrm{A}]_{50}$ | The negative logarithm to base 10 of the $\mathrm{EC}_{50}$ of an agonist. | The term $\mathrm{pD}_{2}$ has also been used, particularly in the earlier literature. |
| Maximal agonist effect, $\alpha$ | 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. <br> 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 <br> 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. |
| $\mathrm{IC}_{50}$ | Either <br> the molar concentration of an antagonist that <br> or reduces a specified response to $50 \%$ of its former value (see also $E C_{50}$ ) 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. <br> The concentration of the radioligand should be stated together with its dissociation equilibrium constant, if known. |
| $\mathrm{pA}_{2}$ | 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, $\mathrm{pA}_{2}$ 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 $\mathrm{pA}_{2}$ and $\mathrm{pK}_{\mathrm{B}}$ coincide only under specific circumstances (see Schild equation, Schild plot and table 7). |

TABLE 5

| Term | Suggested usage | Notes |
| :---: | :---: | :---: |
| 'Concentration' of receptors | [ $R$ ] for nominal concentration of ligand-free receptors; $[R]_{T}$ or $[R]_{\text {tot }}$ for total receptors. |  |
| Number of receptors, $\boldsymbol{N}$ | 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 $\boldsymbol{B}_{\text {max }}$ (the maximal specific binding of a ligand, often expressed in units of mol ligand $/ \mathrm{mg}$ 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. <br> Also referred to as receptor density. |
| Proportion of receptors in specified states | $p_{\mathrm{R}}$ for proportion (fraction) of receptors or binding sites free of ligand. <br> $p_{\text {LR }}$ 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 $p_{\text {LR }}$ refers to the former. <br> $p_{\text {LR }}$. 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 $\mathrm{L}+\mathrm{R} \underset{k-1}{\stackrel{k+1}{\rightleftharpoons}} \mathrm{LR}$ | Units to be specified ( $\mathrm{M}^{-1} \mathrm{~s}^{-1}$ for $k_{+1}, \mathrm{~s}^{-1}$ for $k_{-1}$ in the scheme illustrated). <br> Lower case symbols to be used to denote rate constants (cf., upper case for equilibrium constants). <br> Where there are several ligands, alphabetical subscripts can be added: e.g., $\boldsymbol{k}_{+1 \mathrm{~A}}, \boldsymbol{k}_{-1 \mathrm{~B}}$ |
|  | Here $L$ represents a ligand and $R$ the unoccupied binding site | For more complicated schemes involving several reactions, subscripts $2,3, \ldots$ can be used: e.g., |
|  |  | $\mathbf{A}+\mathbf{R} \underset{k-1}{\stackrel{k+1}{\rightleftharpoons}} \mathbf{A R} \underset{k-2}{\rightleftharpoons} \mathrm{AR}^{*}$ |

## $K$, numerically equal to $k_{-1} / k_{+1}$, and with the



$$
\begin{aligned}
& \text { The word order in dissoclation equiliortum constant is suggested for } \\
& \text { consistency with dissociation rate constant and association rate } \\
& \text { constant. } \\
& \text { The reciprocal (the association equilibrium constant or affinity }
\end{aligned}
$$

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, $\mathrm{M}^{-1}$ ) 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), $\boldsymbol{K}_{\mathbf{d}}$ should be used in preference to $\boldsymbol{K}_{\mathbf{D}}$.
See also Appendix, III.A.

## Described as the Langmuir adsorption isotherm in physical chemistry.

> Although $K$ rather than $K_{\mathbf{L}}$ 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.).

$$
\begin{gathered}
\mathbf{L}+\mathbf{R} \stackrel{\mathbf{K}_{\mathbf{L}}}{\rightleftharpoons} \mathbf{L R} \stackrel{\mathrm{K}_{\mathrm{L}}}{\rightleftharpoons} \mathbf{L R}^{*} \\
\text { The word order in dissociation equilibrium constal }
\end{gathered}
$$

If a subscripted symbol is required when presenting the results of means of ligand binding), $K_{d}$ should be used in preference to
See also Appendix, III.A.


[^1][^2]$$
8
$$

\[

$$
\begin{aligned}
& \mathrm{A}+\mathrm{R} \rightleftharpoons \mathrm{AR} \rightleftharpoons \mathrm{AR}^{*} \\
& \mathrm{~L}+\mathrm{R} \xlongequal{\mathbf{K}_{\mathrm{L}}} \mathrm{LR} \xlongequal{\mathrm{~K}_{\mathrm{L}}} \mathrm{LR}^{*} \\
& K_{14} \quad K_{21}
\end{aligned}
$$
\]

TABLE 6
Terms and procedures used in the analy

| 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: <br> Fade-the waning of a response in the continued presence of agonist. <br> Tachyphylaxis-a decline in the response to repeated applications or doses of agonist. <br> 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. <br> (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: $S_{\mathrm{A}}=e_{\mathrm{A}} p_{\mathrm{AR}}$ |
|  |  | 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. <br> The expression intrinsic efficacy, $\epsilon$, was introduced by Furchgott (1966) to denote the notional efficacy associated with a single receptor: $e=\epsilon[\mathrm{R}]_{\mathrm{T}}$ |
|  |  | in which $[R]_{T}$ indicates the total concentration of receptors. This term is now also used in a wider sense (see paragraph after next). <br> Black and Leff (1983) provided another description of differences in the ability of agonists to produce a maximal effect. They defined the term $\tau$ (tau) as $[\mathrm{R}]_{T} / K_{\mathrm{E}}$, in which $K_{\mathrm{E}}$ 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 tissuedependent 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 Leffs (1983) $\tau$, can still serve as useful comparative measures of the activity of agonists on intact tissues. |

[^3]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. <br> 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 | $p_{\mathrm{AR}}=\frac{[\mathrm{A}]}{K_{\mathrm{A}}\left(1+\frac{[\mathrm{B}]}{K_{\mathrm{B}}}\right)+[\mathrm{A}]}$ | 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. |

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

 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 $\mathrm{pA}_{2}$ (given by the intercept of the unconstrained line) but of $\mathrm{p} K_{\mathrm{B}}$, the negative logarithm of $K_{\mathrm{B}}$, the
dissociation equilibrium constant for the combi



The relationship (Gaddum, 1937, 1943) that replaces the Hill-Langm $A$ and $B$, are in equilibrium with a common
binding site. $P_{A R}$ is the proportion of the binding


The Schild equation

## The Schild plot

## 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

$$
\mathrm{A}+\mathrm{R} \stackrel{K_{1}}{\rightleftharpoons} \mathrm{AR} \stackrel{K_{2}}{\rightleftharpoons} \mathrm{AR}^{*}
$$

the macroscopic dissociation equilibrium constant is given by

$$
K_{\mathrm{eff}}=\frac{K_{1} K_{2}}{1+K_{2}}
$$

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 $K_{\text {eff }}$ 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

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

where $a$ and $b$ are constants. If $a$ is redefined as $-\log _{e}\left(K^{b}\right)$, 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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[^1]:    

[^2]:    equibriam constant, in this table.

[^3]:    Spare receptors,
    receptor reserve

