REVIEW

Pharmacological Onomastics: What's in a name?

TP Kenakin

Biochemical and Cellular Targets, GlaxoSmithKline Research and Development, Research Triangle Park, NC, USA

Drugs are named for their primary receptor target and overt action (agonism, antagonism) but the observation of multiple or collateral efficacies emanating from drugs activating a single receptor target is posing a challenge for drug classification and nomenclature. With increasing abilities to detect alteration in cellular function has come the identification of efficacies that are not necessarily manifest in obvious changes in cell response. Specifically, some agonists selectively activate cellular pathways, demonstrate phenotypic behaviour associated with cell type and some antagonists actively induce receptor internalization without activation. In addition, the effects of allosteric modulators can be linked to the nature of the co-binding ligand posing a similar complication in classification and naming. Thus, accurate labels for this new generation of selective drugs may require identification of receptor partners (G-protein type, β-arrestin) or pathway or, in the case of allosteric modulators, identification of co-binding ligands. The association of distinct phenotypic behaviours with molecules opens the opportunity to better associate clinical effects with distinct pharmacological properties.

Pharmacological onomastics: what's in a name?

A fundamental task of pharmacology is the taxonomy of biologically active molecules and with these classifications comes the task of nomenclature. How a drug is classified and named biases how it is used and misrepresentation of the activity of a drug through misnaming can cause confusion. Drugs are named with a combination of their primary target (for example, a histamine H_1 receptor) and a description of either their directly observed effect (that is, agonist, inverse agonist) or interfering coeffect with another ligand, usually the endogenous ligand (that is, antagonist). In cases where a drug interacts with multiple targets (that is, amitriptylene with activity at histamine H_1, H_2, α_1, muscarinic receptors, catecholamine uptake, phosphodiesterase), the most prominent mechanism (target for which the drug has the highest affinity and/or efficacy) or historically the first mechanism to be discovered often defines the default label for the drug. Multi-target activity also can be labelled for clinical applica-

tion (that is, amitriptylene as an antidepressant). In cases where a collection of molecular mechanisms combine to produce a clinical phenotype, that may also become the label for the drug. For example, the class of drug atypical antipsychotics have a mixture of activities on dopamine D_1, D_2 receptors, histamine H_1, 5-HT$_{2A}$, 5HT$_{1A}$, muscarinic m_1 receptors and α_1-adrenoceptors; these activities combine to determine a clinical phenotype (Goldstein, 2000).

A source of possible complication in nomenclature originates from system-dependent drug behaviour. For agonists, this can involve the strength of the observed agonist effect in any given system, that is, low-efficacy agonists may be antagonists, partial agonists or full agonists in various systems depending on the receptor density and/or efficiency of receptor coupling. This makes labels such as partial agonist and full agonist subjective and, at times, conflicting. System dependence also can be seen with antagonists in the observation of surmountable and insurmountable antagonism. The latter can be a reflection of the kinetics of offset of the antagonist and the temporal characteristics of the assay system. Thus most, if not all, slow offset orthosteric antagonists will demonstrate depression of maximal response (insurmountable apparently non-competitive behaviour) in short window response collections systems such as

Correspondence: Dr TP Kenakin, Biochemical and Cellular Targets, GlaxoSmithKline Research and Development, 5 Moore Dr, Research Triangle Park, NC 27709, USA.
E-mail: Terry.P.Kenakin@gsk.com

FLIPR. These differences highlight the capricious nature of naming drugs for a particular system behaviour.

In general, ambiguities arising from multiple target activity and cell- and assay-dependent variation in drug behaviour are known pharmacological phenomena and usually are dealt with on a case-by-case basis. However, a new aspect of multiple drug activity is emerging from single target-based molecules; the complications arise mainly because of drug efficacy. As a preface to discussion of nomenclature of such drugs, it is worth considering what is meant by the term efficacy and how it has expanded beyond the idea of the initiation of cellular response.

The expectation of efficacy

Historically, a judicious application of Occam's razor has led to a general expectation of zero efficacy in biologically active compounds as a first assumption, that is the default is to assume the most simple idea that a molecule only has affinity for a target. This view has been supported by historical data obtained from systems with limited windows into efficacy, namely overt tissue response observed in real time. When Stephenson (1956) defined efficacy, his indicator was guinea pig ileal contraction and the assumption was that molecules that did not produce contraction, but otherwise interfered with the production of contraction by agonists, were antagonists possessing affinity but not efficacy. The restricted means by which pharmacologists could detect receptor activation at the time limited the number of molecules thought to possess efficacy.

This view had to change with increasing experimental evidence as, for example, when Costa and Herz (1989) revealed an extensive 'secret life' for antagonists as inverse agonists. As recombinant technology became more widespread and constitutively active assay systems became commonplace, the experimental finding was found to coincide with the theoretical prediction, namely that the predominance of antagonists are inverse agonists. For example, in a survey of 322 antagonists (that did not show positive partial agonist activity) for 73 receptors, 85% were found to be inverse agonists with only 15% producing no discernible change in constitutive activity (Kenakin, 2004). In this regard, the availability of assay technology to detect efficacy controls the perception of the presence of efficacy. In general, these data support the view that if a molecule binds to a biological target, there is likelihood that it also will have some sort of efficacy.

The underlying mechanism of the increasing prevalence of efficacy in drug molecules is the obligatory energetic connection between affinity and efficacy, that is if a ligand binds to an ensemble of receptor conformations, it will bias the makeup of that set of conformations to a collection different from what it was before drug binding (Onaran and Costa, 1997; Onaran et al., 2000; Kenakin and Onaran, 2002). This necessarily opens the possibility that one or more of those conformations will interact with cellular components to produce a biological effect. Glimpses into this thermodynamic world have been gained through the study of fluorescently labelled receptors. Specifically, studies with a fluorescent label covalently linked to a β_2-adrenoceptor (such that fluorescence is sensitive to the protein environment) indicate changes in receptor conformation with binding of different types of ligands (Gether et al., 1995; Ghanouni et al., 2001; Palanche et al., 2001; Swaminath et al., 2004). Other generic approaches to the detection of changes in protein conformation and interaction such as bioluminescent resonance energy transfer and fluorescent resonance energy transfer (Bouvier, 2001; Giepmans et al., 2006; Li et al., 2006; Pfleger and Eidne, 2006; Persani et al., 2007) have revealed 'efficacies' not obvious from cellular assay systems. As discussed previously, the prevalence of inverse agonism among the ranks of antagonists also indicates that most antagonists produce changes in receptor conformation.

With increasing means to detect ligand-induced changes in receptor conformation, and cellular responses to those changes in conformation has become expanded definitions of efficacy beyond isolated organ responses (see Figure 1). Even efficacy as the simple definition of induction of cellular response needed to be redefined in light of evidence that receptors form active states in the absence of ligands (constitutive activity). This led to the definition of negative efficacy for inverse agonists and subsequently leads to a general definition of efficacy as the 'property of a molecule that changes the behaviour of the receptor towards the cellular host'.

In general, the evidence supports the view that ligand binding goes hand-in-hand with target modification, that is the presence of efficacy resulting from the formation of a bias towards ligand-stabilized receptor conformations of a single receptor. Given this expanded view of efficacy for biologically active molecules, it is useful to discuss how efficacy relates to the phenomenon of cellular behaviours for multiple receptor conformations.

Single-target pathway pleiotropy

With increasing vantage points that pharmacologists have to view drug activity and dissect signalling pathways, the phenomenon of 'single-target pathway pleiotropy' has been identified. This occurs when certain ligands stabilize different receptor active states which then go on to activate a number of different cellular processes (Kenakin, 1995a, 2002; Urban et al., 2007). These ligands become associated with biased activation of these processes and thus take on cell-specific phenotypic behaviour. The fact that some molecules in a general class (that is, agonists) take on specific behaviours in systems can lead to ambiguous nomenclature and the emergence of cell-specific aliases. These behaviours occur when the ligand-bound receptor activates some, but not all, of its repertoire of cellular pathways.

For receptors that interact with more than one G-protein in the cell, different agonists can produce selective G-protein activation. This phenomenon has been given various names from 'stimulus trafficking', 'biased agonism' to 'functional selectivity'. For example, calcitonin receptor-activating ligands such as porcine calcitonin can preferentially activate G_s protein (over G_i proteins) when compared to agonist such
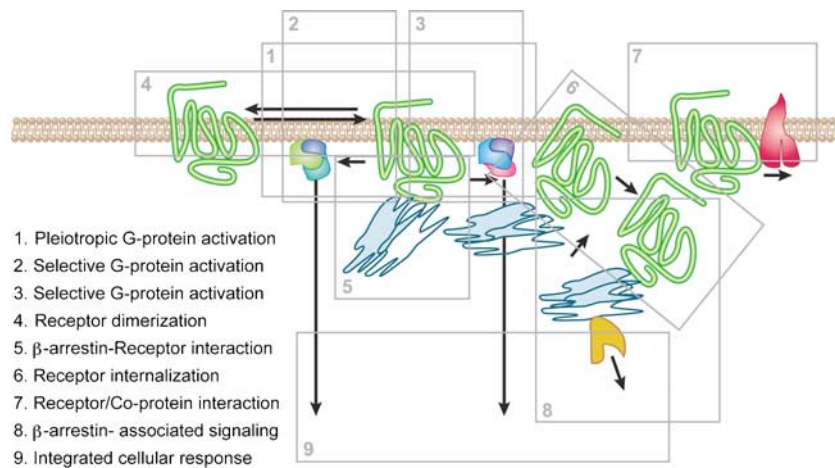
Figure 1 A sample of interactions of seven transmembrane receptors with cellular components to generate phenotypes of efficacy. Specific assays are available to isolate these processes and define molecular activity associated with them. It should be noted that cellular response does not automatically indicate interactions of the ligand-bound receptor with some of these processes (that is, is not a universal indicator of molecular efficacy).

as rat amylin (Watson *et al.*, 2000), a bias in the cellular signal activation is produced. Pleiotropic G-protein interaction can be more pronounced as in the case of the CB_1 cannabinoid ligand desacetyllevonantradol, which is a 'positive' agonist for G_{i1} and G_{i2} but an 'inverse' agonist for G_{i3}. Similarly, (*R*)-methanandamide is an 'inverse' agonist for G_{i1} and G_{i2} and a 'positive' agonist for G_{i3} (Mukhopadhyay and Howlett, 2005). Therefore, the labels positive and inverse agonist are both associated with the ligand and CB_1 receptor but for different G-protein pathways. A nomenclature based on simple target-centric behaviour for (*R*)-methanandamide as a cannabinoid receptor agonist breaks down; depending on the receptor coupling partner, this molecule can legitimately be called an agonist or an inverse agonist.

Selective pathway interaction goes beyond the G-protein level. As assays enable observation of activities deeper into the cytoplasm, other 7TM receptor ligand-induced signalling differences are observed. The discovery that β-arrestins bind to phosphorylated receptors to function as signalling scaffolds for kinases (Lefkowitz, 2004; Terrillon and Bouvier, 2004; Lefkowitz and Shenoy, 2005; Luttrell, 2005, Lefkowitz *et al.*, 2006) opens a new G-protein-independent signalling paradigm for 7TM receptors. It can now be shown that many receptors activate cellular kinases through separate pathways. For example, parathyroid hormone (PTH) activates extracellular signal-related kinase through separate G-protein-related and G-protein-independent pathways. The intriguing and pharmacologically relevant aspect to this effect is that the chemical structure of the agonist may be a control point for the selective activation of these processes. Thus, analogues of PTH can induce separate activation of each pathway with the selective stimulation of G-protein-mediated extracellular signal related kinase (ERK)1/2 stimulation by [Trp^1]PTHrp-(1–36) and selective stimulation of β-arrestin-dependent stimulation of ERK1/2 by PTH-1A ([D-Trp^{12},Tyr^{34}]PTH-(7–34); Gesty-Palmer *et al.*, 2006, see Figure 2). Similarly in another receptor system, the Substance P analogue SpD ([D-Arg^1,D-Phe^5,D-Trp^{7,9},Leu^{11}]Substance P)
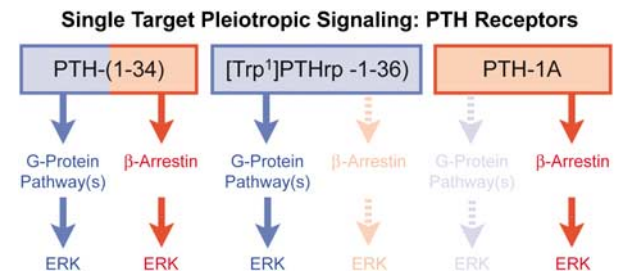
Figure 2 Schematic diagram of parathyroid hormone (PTH) and analogues as activators of two separate pathways for extracellular signal kinase activation, namely G-protein-dependent (blue) and β-arrestin G-protein-independent (red). PTH-1A = [D-Trp^{12},Tyr^{34}] PTH-(7–34). Data from Gesty-Palmer *et al.* (2006).
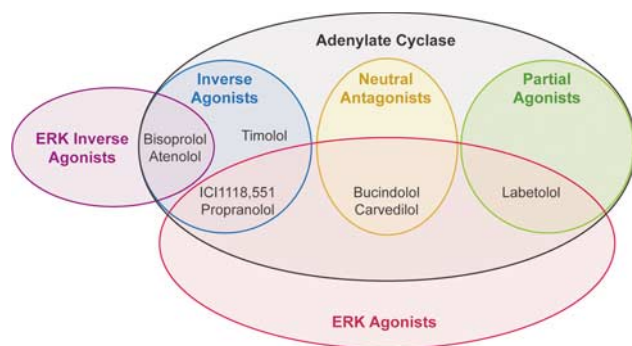
and bombesin are both agonists of the bombesin/gastrin-releasing peptide receptor producing ERK1/2 activation. However, the effects of SpD are pertussis sensitive (indicating a G_i-protein dependence of the effect) while the response due to bombesin is not. This latter agonist traffics stimulus directly to the ERK1/2 pathway through a G-protein-independent β-arrestin effect (Mackinnon *et al.*, 2001). Thus, while both SpD and bombesin are agonists of the same receptor, they induce response through different pathways.

New cellular eyes to see also have revealed efficacies not immediately evident, such as the active internalization of receptors by antagonists. For a number of years it had been observed that serotonin antagonists produce effects consistent with the active internalization of receptors (Gray and Roth, 2001). The advent of technology enabling the visualization of receptor internalization has since definitively shown that antagonists, for a number of different receptors, produce no measurable receptor activation but still actively internalize receptors. Like inverse agonism, this is another hidden efficacy of antagonists, made evident by the appropriate assay. In the case of antagonists, added properties currently not explicitly associated with certain molecules, can result in cellular and clinical phenotypes. For example, the known ability of inverse agonists to induce cell

surface upregulation (Milligan and Bond, 1997) can lead to tolerance as in the treatment of ulcer with clinically used histamine H_2 antagonists (Smit *et al.*, 1996). Thus, a case could be made for differentiating antagonists on the basis of efficacy that causes changes in cell surface receptor regulation. For example, 5-HT_{2A} antagonists that induce receptor internalization (that is, clozapine: Willins *et al.*, 1999; mianserin, ritanserin: Bhatnagar *et al.*, 2001) should be differentiated from those that induce receptor upregulation (MDL 11939 [α-phenyl-2-(2-phenylmethyl)-4-piperidine-methanol], Aloyo *et al.*, 2001).

With the introduction of new technologies that enable viewing of drug-induced biological activity from numerous vantage points, multiple behaviours are increasingly being discovered leading to a log jam in nomenclature. For example, the β-blocker propranolol reveals different activities when tested in different systems being an inverse agonist with respect to G_s-protein activation and a positive agonist with respect to ERK1/2 activation (Azzi *et al.*, 2003; Baker *et al.*, 2003). These discoveries of multiple behaviours bring complications in nomenclature, that is propranolol lays legitimate claim to being a β-blocker, inverse agonist for G_s-protein and and ERK1/2 agonist. An extensive examination of eight ligands on β_1- and β_2-mediated activation of adenylate cyclase and mitogen-activated protein kinase activity reveals a rich texture of positive, and inverse agonism as well as neutral antagonism for the various pathways (Galandrin and Bouvier, 2006). These data and data for propranolol were used to construct Figure 3 to show how these various ligands can be distinguished through their varying efficacies for these pathways. The activity of interest is in the eye of the beholder and the beholder then chooses the alias for the drug.

The stabilization of different receptor conformations, or ensemble of conformations of receptor, by molecules forms the basis of a system where molecules may not have a single efficacy, but rather possibly numerous efficacies depending on the biological activity of the various conformations enriched by the molecule. This has been referred to as 'collateral efficacy', meaning effects produced in parallel and belonging to the same but not in a direct line of descent and not secondary in nature (Kenakin, 2006). Another description used for ligands involved with β-arrestin ERK and G-protein signalling is 'pluridimensional efficacy' (Galandrin and Bouvier, 2006) suggesting multiple efficacies for a single molecule activating a single target. In light of these multiple behaviours, efficacy may require qualification and a formalized convention for nomenclature. In addition to efficacy-based complications in drug nomenclature, the same problem arises with molecules that are permissive in their receptor effects with other molecules, namely, allosteric modulators.

Allosteric modulators as pharmacologic chameleons

Allosteric modulators are molecules that co-bind to the receptor with other molecules and, as such, their effects can be probe-dependent. For example, the m_2 muscarinic receptor allosteric ligand eburnamonine produces potentiation of affinity to pilocarpine, no change in the affinity of arecaidine propyl ester and reduction of affinity to arecoline (Jakubic *et al.*, 1997). What is such a ligand to be called? In this case, the name is dependent on the co-interacting molecule. Another unique aspect of allosteric molecules is that, since their effects emanate from an interaction at a separate site on the receptor, they have saturable effect when the allosteric site is completely occupied. This results in finite effects on the affinity and efficacy of the co-binding ligand. Whereas competitive antagonists completely block the effects of agonists, if present in adequate concentrations, an allosteric modulator may produce only a mild effect on agonist effect allowing the tissue to still respond but at a lower intensity. For example, an allosteric modulator with a co-operative constant α of 0.3 produces a threefold decrease in agonist affinity and this will be the maximal effect on the agonist. In these cases, the term modulator is an important distinction from the term antagonist.

How important is descriptive nomenclature?

Over the past 15 years, evidence has accumulated to show that molecules can have efficacies not evident from studies in conventional biological response-orientated assays and that these efficacies are often pluridimensional. The corollary to this idea is that not all possible efficacies reside in every molecule for a given target. This results in a texture for agonism, antagonism, modulation and potentiation for a range of cellular processes; the question then is, should names be associated with these molecules to identify pharmacological uniqueness? An analogy can be drawn to describing a person as a musician in a general sense and then progressively defining more accurately that person's function with successive modifiers such as stringed instrumentalist then a guitarist, then electric guitarist and so on.

There are tangible benefits from uniquely identifying drugs that do different things to biological systems. Specifically, this can assist in the process of linking therapeutic value to pharmacological properties through translational

Figure 3 The classification of β_2-adrenoceptor ligands. Eight β_2-adrenoceptor ligands can be distinguished as positive and inverse agonists and neutral antagonists for adenylate cyclase (Gs-protein-mediated response) and agonists or inverse agonists for ERK1/2 signalling. Data from Galandrin and Bouvier (2006), Azzi *et al.* (2003) and Baker *et al.* (2003).

medicine (Littman *et al.*, 2007). One line of reasoning for this approach argues that if a molecule is biologically active, it is evident that it changes the ensemble of receptor conformations. Therefore it follows that there is a likelihood that it may have efficacies for other systems associated with that target. The value of characterizing this efficacy would be evident in the association of the collection of activities with a clinical phenotype.

The need to identify special ligand activity is balanced by the need to simplify behaviour-rooted systems of nomenclature. One approach would be to label according to observed biological phenotype, that is the previously mentioned typical and atypical antipsychotics. For example, agonists activating ERK pathways through G-proteins and independently through β-arrestin can be separated in terms of the observed response patterns. The former demonstrates intense but short-lived response while the latter produce lower intensity more prolonged responses. However, the problem with these phenotypes is the possibility of mixed actions (that is, PTH does both and shows an intense but prolonged response).

Another problem with phenotype-based labelling is the possible divergence from target dependence and emergence of cellular dependence of these phenotypes. For example, receptor desensitization and internalization is an important issue for opioid analgesia (some opioid agonists desensitize receptors more than others) and in some cases the differences between opioid agonists is profound as in the clear inability of the μ-opioid receptor agonist herkinorin to cause the receptor to interact with β-arrestin or to internalize (Groer *et al.*, 2007). However, there is cell type dependence for desensitization and internalization observed for many other opioid agonists (Marie *et al.*, 2006) and this would lead to confusion in phenotype-based classification. Similarly, while some CCR5 ligands produce receptor internalization, an activity that may be relevant in protection against HIV-1 entry, CCR5 internalization varies with the variety of cells used for the experiments therefore the phenotype of receptor internalization is variable with cell type. Cell-specific phenotypic behaviour is fragile and different phenotypes could emerge from something as simple as receptor density. For example, the opioid agonist [D-Ala^2-D-Leu^5]-enkephalin produces inhibition of adenylate cyclase and stimulation of high-affinity GTPase in NG 108–115 cells. However, diminution of receptor number through alkylation soon removes the more sensitive GTPase response and changes the phenotype to only adenylate cyclase inhibition (Costa *et al.*, 1988).

There are cases where a term has been used to identify unique activity. For example, protean agonists, defined in theoretical terms, are molecules that produce an active state of the receptor that is of lower efficacy than the state formed constitutively in the absence of agonists (Kenakin, 1995b, 2001). Under these circumstances, they are partial agonists in non-constitutively active systems and inverse agonists in constitutively active systems; these molecules would function as the ultimate normalizers *in vivo*. Thus, dichloroisoproterenol is a β-adrenoceptor partial agonist with the legitimate alias protean agonist as well (Chidiac *et al.*, 1996). Such molecular-mechanism-based monikers can be useful differentiators for unique activity. Figure 4 shows the effect of four different molecular types of ligand on an *in vivo* constitutively active system with endogenous tone. It can be seen that different levels of effect are seen with a partial agonist, neutral antagonist, protean agonist and inverse agonist. In an *in vitro* non-constitutively active system, the partial and protean agonists and, separately, the inverse agonists and neutral antagonists would give similar profiles and be non-differentiable. This highlights the importance of using appropriate assays to characterize ligand activity.

At present, there is no systematic naming convention for distinguishing single-target uniqueness; this may be a topic for future consideration. Attempts have been made in some cases, such as protean agonism and ago-antagonism. This latter term, which has been previously used to label opposing muscle spindle inputs in physiology (Ribot-Ciscar and Roll, 1998) and separately as opposing 'ying yang' hormones such as vasopressin and oxytocin (Legros, 2001), for single targets refers to molecules that are positive agonists for one pathway (that is, G-protein) and antagonists (or inverse agonists) at another (Beyermann *et al.*, 2007). Similarly, ago-allosteric modulators refer to agonists that also potentiate endogenous agonist action (Schwartz and Holst, 2006). While these terms suffer from the same
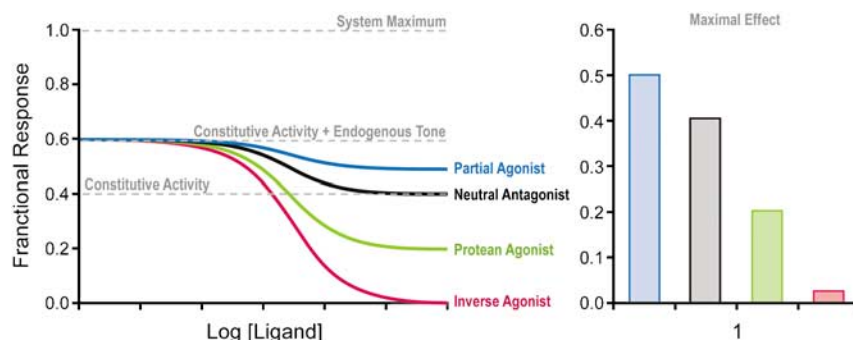
Figure 4 Hypothetical dose–response curves for four molecules with different patterns of efficacy. The system is constitutively active (fractional effect = 0.4) and then placed under an additional endogenous agonist tone to a level of 0.6 fractional effect. A partial agonist decreases the endogenous tone but imposes its own intrinsic activity on the system, a neutral competitive antagonist abolishes the endogenous tone but does not eliminate constitutive activity, a protean agonist reduces the constitutive activity somewhat but imposes its own intrinsic effect and an inverse agonist abolishes both the endogenous tone and the constitutive activity.

shortcoming as other system-based labels (the bias in the cellular pleiotropic G-protein content may define the primary observed activity), it also identifies ligands as being different from standard agonists.

Naming biased-agonists and other pluridimensional ligands becomes complicated by the need to identify not only the primary receptor and overt action, but also complimentary players such as couplers (that is, G-proteins) and/or signalling pathways. In the case of allosteric ligands, co-ligand names may be required to describe succinctly effects although it could be argued that only the effects on endogenous agonist need be considered. However, in areas such as the chemokine system where there is redundancy in ligands for receptors (Wells *et al.*, 2006), this may still pose a practical problem even for endogenous ligands. For example, the allosteric HIV-1 entry inhibitor aplaviroc blocks the binding of the natural chemokine MIP-1α but does not block the binding of RANTES, another natural chemokine agonist for this receptor (Watson *et al.*, 2005). Probe dependence may be quite pronounced as in the case of the complete resistance of CXCR4-mediated chemotaxis response to the stromal-derived factor type 1α peptide fragments [Ala-Ser-Leu-Trp] and [Arg-Ser-Val-Met] to antagonism by the CXCR4 antagonist AMD-3100 (Sachpatzidis *et al.*, 2003).

Conclusions

The accurate determination of nuances in ligand efficacy may yield important patterns that can be characterized *in vitro* in experimental systems and then associated with useful therapeutic profiles in more complex *in vivo* systems. The binning of molecules into categories (that is, as in the case of ERK1/2 agonist—β-blockers, see Figure 3) is the result of testing of biologically active molecules in numerous pharmacological assay systems; the thermodynamic association of affinity and efficacy would advocate rationale for such extensive testing. This suggests that an important part of drug taxonomy is to define 'completely' the efficacies of a given biologically active molecule with as many eyes to see activity as possible. This also suggests that the classification of drugs is an ongoing conditional process either with respect to the signalling pathway connected to the receptor and/or the orthosteric molecule co-binding to that receptor. The potential bonus of the identification of collateral or pluridimensional efficacy furnishes the justification. A concomitant system of nomenclature would assist in this process as appropriate labels for drugs would bias how the molecule is used.

Conflict of interest

The author states no conflict of interest.

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