Published in final edited form as:

Trends Pharmacol Sci. 2007 August ; 28(8): 390–396. doi:10.1016/j.tips.2007.06.002.

GPCR functional selectivity has therapeutic impact

Richard B. Mailman

Departments of Pharmacology, Psychiatry, Neurology, and Medicinal Chemistry, University of North Carolina, Chapel Hill, NC

Abstract

A plethora of *in vitro* data have shown that certain ligands may have the property of causing differential activation of signaling pathways mediated via a single receptor (“functional selectivity”). It remains unclear, however, whether functionally selective properties are meaningful *in vivo*. Data with experimental compounds that are functionally selective at the dopamine D_{2L} receptor *in vitro* suggest that these properties may predict their atypical behavioral actions. Moreover, the novel antipsychotic drug aripiprazole is commonly believed to be a D₂ partial agonist, yet data clearly show aripiprazole is functionally selective *in vitro*. It is proposed that the effects of aripiprazole in animals and man can only be reconciled with its functionally selective D₂ properties, not its partial D₂ agonism. Together, these data provide support for the hypothesis that compounds with functionally selective properties *in vitro* are likely to have novel actions *in vivo*, opening doors to new avenues of drug discovery.

This issue of *TiPS* contains a series of outstanding theoretical pieces that relate to new concepts about the functional actions of GPCR/7TM receptors. Many laboratories have converged on this arena via studies of GPCRs or GPCR-related signaling mechanisms, and the articles in this issue have provided elegant commentary on some of the molecular mechanisms that now attract wide interest. This emerging research has led to reconsideration of some fundamental concepts of receptor pharmacology. As an example, Violin and Lefkowitz (this issue) note that “*until recently, drug efficacies for G protein activations and β -arrestin recruitment were believed to be highly correlated, restricting 7TMR response to a linear range of effects from stimulatory to inhibitory.*” Related to this was the notion that a drug acting via a single receptor could always be categorized by its degree of linear response (i.e., a drug was an agonist, partial agonist, or an antagonist). This led to the concept of “intrinsic efficacy” [1] that described the inherent functional properties of a drug at a specific target receptor. Intrinsic efficacy is not to be confused with operational terms like “intrinsic activity” [2] or “efficacy” [3] that reflect the measured response in any particular receptor functional system.

Although the idea of intrinsic efficacy has been highly ingrained, more than a decade ago data began emerging that was seemingly irreconcilable with this premise. Examples included situations where the relative intrinsic activity of two partial agonists at two functional endpoints was reversed, to cases where a single drug caused both full agonist and antagonist effects mediated by the same receptor [for review, see 4]. This phenomenon was been given a plethora of names [4,5], but for the purposes of this piece we shall term it “functional selectivity.”

Corresponding Author: Richard B. Mailman, CB#7160, 7011 NC Neurosciences Hospital, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7160 USA, richard_mailman@med.unc.edu, Phone 919-966-2484 Fax 919-966-9604.

Conflict of interest: Richard Mailman and the University of North Carolina have a financial interest in BioValve Technologies, the licensee of technology that includes dihydroxidine and propylDHX that are discussed in this Review. The opinions here are those only of the author, and do not represent the views of the University of North Carolina, BioValve Technologies, or any other party.

We were one of several laboratories that contemporaneously stumbled into this arena during our research on the most proximal aspect of receptor pharmacology – how ligands interacted with their targets, and how one could design “better” ligands from such knowledge. Because our work focused on dopamine receptors, study of dopaminergic ligands offered the “benefit” of commonly used behavioral assays whose pharmacology was well understood. Thus, when we found unexpected behavioral effects of a drug with functionally selective properties *in vitro*, the profound pharmacological ramifications were immediately clear.

Our data impressed us sufficiently that at a 1996 dopamine receptor meeting held in Ankara, I said that “...the “functional selectivity” hypothesis [is] the concept that [some] drugs can cause functional multiplicity even when interacting with a single receptor isoform. The foundation of this hypothesis is extensive data showing that some drugs can bind to a single receptor isoform, yet cause distinct functional changes depending on the cellular localization of the receptor-G protein complex. One mechanism for functional selectivity may be atypical conformation changes [when compared to the endogenous ligand] induced when such drugs bind to the receptor-G protein complex. These distinct conformation changes force the dissociation of some, but not all, receptor-G-protein complexes (depending on the G-protein to which the receptor is coupled). The particular type(s) of G-protein are dependent on both the type of cell, and the location in the cell, where the receptor of interest is located. Such functional targeting allows drug effects to be refined to a degree not possible just by targeting specific receptor isoforms. This could yield important therapeutic advances, although it introduces a new level of complexity that will require significantly greater understanding of receptor dynamics and the interaction with transduction mechanisms.” [from the published proceedings in 6].

A priori, I would like to describe why I favor the term “functional selectivity” that we first used publicly in the early 1990's [7]. The existence and potential impact of functional selectivity was realized by many laboratories studying different receptor systems, most of whom became sufficiently engaged by their observations that they coined their own term [4,5]. Functional selectivity was appealing to us because it was operational, and because it accommodated a variety of mechanisms both proximal (related to the ligand and its receptor target) and distal (e.g., oligomerized receptors, G proteins, other signaling molecules, scaffolding proteins, etc.). Some terms (e.g., “trafficking”) imply mechanisms that may not always be relevant. Other phrases used the word “agonist” (e.g., “protean agonist” or “agonist trafficking”) and cannot accommodate those rarer cases when a ligand has both agonist and pure antagonist actions at different functions mediated via a single receptor. Although we recently proffered an alternative (ligand-induced differential signaling) that had an easy acronym (LIDS) [4], until IUPHAR conventionalizes the terminology, the reader will excuse our continued use of “functional selectivity” knowing that it refers to phenomena discussed in this issue and elsewhere recently [4,8].

Whatever the debate about terminology, the research summarized in this issue of TiPS should remove all doubt that the phenomenon of functional selectivity is real, and that the relevant mechanisms are intriguing. What may be less obvious is that this phenomenon also can provide a route to truly novel drugs that could never have been conceptualized based on classic principles of pharmacology. Although ironclad mechanistic proof for this assertion is not yet in hand, an experimental trail that began in the late 1980's convinced us that functional selectivity will profoundly influence drug discovery.

Stumbling onto functional selectivity

By the late 1970's, it was generally accepted that there were at least two major classes of dopamine receptors [9], D₁ and D₂ [10], that now are known to be products of five genes

[11]. Although many thought that the D₁ receptor was “a receptor in search of a function” [12], we hypothesized that dopamine D₁ full agonists might have great utility as a novel therapy for Parkinson's disease [13,14]. Prior tests with D₁ agonists had not been promising [15,16], but those compounds were partial agonists, and a variety of data suggested a full agonist might be qualitatively and quantitatively different. These results were one trigger for our efforts to understand how ligands interacted with and activated D₁ receptors [17,18].

One hypothesis guiding this early research was the notion that both high D₁ affinity and selectivity for D₁ versus D₂ receptors required a ligand to occupy an “hydrophobic accessory region” of the D₁ receptor [18-21]. When we discovered the first bioavailable full D₁ agonist dihydrexidine, it had the predicted D₁ affinity and functional properties [22] and profound antiparkinson effects [14,23], yet it was only ten-fold D₁:D₂ selective [24,25]. Although the antiparkinson effects of dihydrexidine occurred at low doses expected to favor D₁ occupation [23], the dogma about the role of D₂ receptors in antiparkinson actions made it critical to study this further.

The binding curve for dihydrexidine to brain D₂ receptors was shallow and guanine-nucleotide-sensitive, suggesting that the drug was a typical full D₂ agonist with properties similar to the prototypical D₂ agonist quinpirole [25]. Yet there was an immediate conundrum. Drugs that are full agonists at both D₁ and D₂ receptors should have behavioral effects similar to indirect dopamine agonists that increase synaptic concentrations of dopamine (e.g., amphetamine or cocaine) since all dopamine receptors should be activated. Yet when dihydrexidine was given to rats, even at very high doses, the behavioral effects largely reflected only D₁ properties [26]. Similarly, in normal monkeys, dihydrexidine caused few overt changes in behavior of the type that would be expected for either D₂ agonists or for indirect dopamine agonists.

Could the functional actions of dihydrexidine at D₂ receptors explain these atypical behavioral properties? At D₂ receptors in rat striatum or in expressed human D_{2L} receptors, both dihydrexidine and N-n-propyldihydrexidine (propylDHX, an analog that is several hundred-fold more D₂:D₁ selective) inhibited forskolin-stimulated adenylate cyclase activity with full intrinsic activity, effects blocked by selective D₂ antagonists. Similar D₂ agonist properties were observed *in situ* in terms of inhibiting prolactin secretion. Yet unexpectedly, dihydrexidine and propylDHX failed to activate those D₂-like autoreceptors mediating inhibition of cell firing, dopamine release, or dopamine synthesis. Indeed, high doses of dihydrexidine were ineffective at activating the D₂-like autoreceptors that inhibit the firing of nigral neurons, yet attenuated the effects of apomorphine, a potent D₂ agonist in this assay [27]. These functional anomalies were not related to differences in binding of dihydrexidine [27].

Thus, these early data suggested that dihydrexidine and propylDHX had high intrinsic activity at postsynaptic D₂-like receptors, but low intrinsic activity at presynaptic receptors [28]. What might have caused such an unexpected pattern of effects? It was unlikely this was a result of a non-dopamine receptor, based on receptor screening and the agonist-antagonist functional studies that were done [25]. Another possibility came from the contemporaneous cloning of the D₂-like receptors (D_{2L}, D_{2S}, D₃) and their localization in specific cell types and regions in brain [for review, see 11]. It might be that dihydrexidine was an agonist at one dopamine receptor isoform (e.g., D_{2L}), but an antagonist at another (e.g., D_{2S} or D₃). This explanation for the functional discrimination was supported neither by studies with heterologously expressed receptors, nor by emerging neurobiological information about these three receptors. There was a third possible mechanism: functional discrimination was caused by differences in receptor reserve. It was known that there is higher presynaptic receptor reserve that causes increased the potency and efficacy of partial agonists [29]. Yet this actually deepened the

paradox –dihydropyridine had greater D₂ functional activity postsynaptically, the opposite of predictions based on receptor reserve!

Eureka?

Conceptual breakthroughs are often envisioned to be like Archimedes' naked dash through Syracuse. In our case it was more like Isaac Asimov's description – "*The ... phrase ... that heralds new discoveries, is not 'Eureka!' - but 'That's funny...'*" How could it be that a single molecule could have agonist and antagonist effects mediated via the same receptor? This idea seemed heretical in terms of the classic pharmacological concept of intrinsic efficacy [3], an idea that has led us to teach that a ligand is an agonist OR a partial agonist OR a neutral antagonist/inverse agonist. The clue was in a conceptual advance then known as GPCR promiscuity: GPCR signaling involving different signaling partners could mediate alternate signaling pathways [30].

This was a hint to a plausible mechanism. One could conceive a ligand or drug as targeting not the receptor alone, but a receptor-directed signaling complex. A synthetic ligand might very well engage and/or perturb different aspects of a receptor than the endogenous ligand based on its unique structural features. This would result in ligand-specific conformational changes that also were influenced by the local signaling partners of the target receptors. For example, a ligand like dihydropyridine or propylDHP would induce different conformational changes in a D_{2L} receptor than would dopamine or quinpirole. Since the actual target was not the D₂ receptor, but several different D₂-linked signaling complexes, it was possible for there to be differential activation of one signaling pathway versus another.

By early 1993, this hypothesis provided a parsimonious explanation for the body of phenomenological evidence that we had accumulated. Our first attempts to publish these data, however, were quite unsuccessful. The reviewers were unanimous in their view that drugs cannot be agonists and antagonists at the same receptor, and that our results must be an artifact. Clearly we needed a simpler model system to test this hypothesis further. The hurdle was finding a clonal *in vitro* system in which we could manipulate dopamine receptor expression, but in which transfected D₂ receptors would couple to functions that were mechanistically analogous to those we had studied *in situ*. The first such system was the pituitary lactotroph that expresses only products of the D₂ gene (DADR2), and that provided two functional endpoints that paralleled those studied *in situ*. As in heterologously expressed D₂ receptors, dihydropyridine was a full agonist at inhibiting adenylate cyclase, with effects blocked by D₂, but not D₁, antagonists. Conversely, dihydropyridine had little intrinsic activity at D₂ receptors coupled to G protein-coupled inwardly-rectifying potassium channels (GIRK), and was an effective antagonist of the functional actions of dopamine in the lactotroph [27]. Here again, dihydropyridine acted as an agonist and antagonist in the same cell.

Soon thereafter, there were reports of a mesencephalic-derived cell line (MN9D) in which transfection of the D_{2L} receptor led to coupling of the receptor to inhibition of adenylate cyclase and inhibition of dopamine release as occurs in dopamine neurons [31,32]. Neither dihydropyridine nor propylDHP had effects in untransfected MN9D cells, but after D_{2L}-transfection both compounds were full agonists at inhibition of adenylate cyclase activity, effects blocked by D₂, but not D₁, antagonists. Conversely, the full D₂ agonist quinpirole inhibited the depolarization-induced release of dopamine in a concentration-responsive, antagonist-reversible, fashion, but neither dihydropyridine, nor propylDHP, inhibited dopamine release. Moreover, propylDHP actually antagonized the effects of quinpirole. Aspects of these data are summarized in Figure 1. The possibility that differences in receptor reserve (*vide supra*) within the same cell contributed to these findings was ruled out by the fact that the

norpropylapomorphine isomer SNPA actually had the reverse functional selectivity profile of dihydrexidine or propylDHX [33].

The body of this and later work convinced us that “functional selectivity” with dihydrexidine and its analogs at the D_{2L} receptor was “real,” [6,27,28,33,35,36], setting the stage for a focus on involved mechanisms (e.g., “conformational induction” vs. “drug-active state selection”, etc.) highlighted elsewhere in this issue of TiPS.

Does functional selectivity really matter *in vivo*?

Although functional selectivity opens a host of interesting mechanistic doors, one could suppose that the types of results we have discussed, as well as similar ones found in many other receptor systems [4], are of little more than heuristic interest. The fact that our initial studies included data from both *ex vivo* and *in vivo* studies suggested to us, however, that these findings were not only mechanistically interesting, but of profound potential pharmacological impact. We tested this idea by characterizing the behavioral effects of propylDHX which as noted above was a functionally selective D₂ ligand *in vitro*. Classic pharmacology would have predicted that a compound with full intrinsic activity at D₂-mediated adenylate cyclases would have behavioral effects very similar to drugs like the prototypical D₂ agonist quinpirole. Typical D₂ selective or D₂/D₃ agonists have biphasic effects, causing locomotor inhibition at low doses and locomotor stimulation at higher doses [37]. Yet propylDHX only caused modest locomotor inhibition across a wide range of doses, with no competing behaviors that might have interfered with locomotion [38]. To us, this provided additional support for the hypothesis that functionally selective compounds would have novel pharmacological actions. As it turned out, this idea was timely and of particular relevance to novel approaches being developed to treat schizophrenia.

D₂ receptors and agonist treatment of schizophrenia

The serendipitous observations that led to the discovery of chlorpromazine [39] allowed discovery that such antipsychotic effects were due to antidopaminergic actions [40]. This was later shown to result from blockade of D₂, not D₁, dopamine receptors [41]. As of this date, there is no effective antipsychotic drug that does not have D₂ antagonism as part of its pharmacological profile (albeit, see discussion of aripiprazole below). These findings led to what might seem a paradoxical hypothesis: therapeutic benefit might result from a D₂ dopamine agonist. Pharmacologically this actually was quite rational: if one could activate autoreceptors preferentially with a dopamine agonist, one might decrease dopamine neurotransmission and thus have a dopamine antagonist-like effect [42].

Dopamine neurons express both high densities of D₂ and low densities of D₃ autoreceptors. Activation of these autoreceptors (e.g., with dopamine) causes a decrease in both synthesis and release of dopamine, as well as the firing of dopamine neurons. Dopamine and D₂ agonists have higher potency at autoreceptors than at postsynaptic receptors due in large measure to the greater degree of presynaptic receptor reserve [29]. This is thought to explain why the behavioral response to a full D₂ agonist is typically biphasic with respect to dose, with inhibition seen at low doses (the result of autoreceptor stimulation) and stimulation at higher doses (direct postsynaptic activation). In theory, one could use a low dose of a full agonist to achieve this selective presynaptic activation, thus causing benefit in schizophrenia. Although several promising reports suggested that a full agonist might fulfill this theoretical promise [43-46], in practice the use of full agonists alone or as adjuncts to D₂ antagonists has not worked. In retrospect, this may have been because temporal fluctuations in drug levels *in situ* would make it difficult to achieve the “right” relative receptor occupancies to give selective presynaptic effects.

One way to overcome this was the use of partial agonists that are known to have low intrinsic activity in systems with little receptor reserve, but significant intrinsic activity at the same receptor in a system with high receptor reserve [47]. Several lines of preclinical evidence suggested that partial agonists might be a way to address this issue of selective presynaptic dopamine inhibition. A plethora of *in vitro* and animal studies suggested that one such drug, (-)-3-PPP (preclamol), might be an excellent candidate. Despite reports of short term efficacy, the benefits were short lived [48,49]. It was this backdrop that brought functional selectivity to the clinical arena.

Functional selectivity and schizophrenia: is aripiprazole a D₂ partial agonist or the first functionally selective clinical drug?

Aripiprazole is the newest approved antipsychotic drug proffered by its developers as the first approved high affinity, low intrinsic activity partial D₂ agonist. Although the compound has effects on several other receptors, many of the leading figures in schizophrenia biology have taken to calling aripiprazole the first “dopamine stabilizer” based on its D₂ partial agonist properties [50-52]. According to this view, in situations of high extracellular dopamine concentrations (e.g., in mesolimbic areas involved in positive symptoms), the partial agonist properties of aripiprazole compete with dopamine and cause partial antagonism offering clinical benefit. Conversely, in situations where extracellular dopamine concentrations are low (for example in dopamine circuits involved in working memory), the drug can occupy additional receptors and cause partial activation. On its face, this is a cogent argument, combining classic pharmacological logic about mechanisms of partial agonism with recent information about the biology of schizophrenia.

There is no doubt that in many assay systems, aripiprazole looks like a low-to-moderate intrinsic activity partial agonist [53-55] as required by this prevalent hypothesis. On the other hand, some of the available data are difficult to reconcile with this hypothesis. First, the intrinsic activity and potency of aripiprazole for the D₂-mediated inhibition of cAMP accumulation is cell line-dependent. The drug demonstrates weak partial agonist activity in the CHO-D_{2L} cell line, but strong partial agonist activity in HEK-D_{2L} cells [53-55]. Another example of this is shown in Figure 1 (left panel) where aripiprazole has markedly different potencies at two D_{2L}-mediated functions within the same cell line [34]. Moreover, in some systems, aripiprazole completely antagonizes both D₂ agonist-mediated GTP γ S binding and GIRK channel activity [55], while acting as a full agonist *in situ* for D₂-mediated inhibition of tyrosine hydroxylase [56]. Thus aripiprazole appears to elicit D₂-mediated functional effects that encompass the whole range of classic pharmacological traits. It is such large variations in intrinsic activity and/or potency, not explicable by other mechanisms, that suggest the drug is “functionally selective” [4] and not a simple partial agonist. The question is how this relates to the actions of aripiprazole *in vivo*.

On the one hand, if one accepts the notion of functional selectivity, all of the available animal and clinical behavioral data presumably resulting from a partial agonist mechanism can be explained equally well by functional selectivity. On the other hand, there are a few pieces of such data that are irreconcilable with the partial agonist hypothesis. One of the clearest of these are the effects of aripiprazole in the unilaterally lesioned 6-hydroxydopamine (6-OHDA) treated rat [57], first thought of as a possible rat model of Parkinson's disease. Both full and partial dopamine agonists cause the test animal to turn with high frequency in a tight circle towards the side away from the lesion (i.e., leftward turning if the lesion was on the right-side nigrostriatal pathway). The robust rotation in this model is a result of relative receptor/cellular hypersensitivity of the target receptors on the lesioned, dopamine-depleted, side. As a partial agonist, aripiprazole also should cause such rotations, but it does not [56]. Moreover, it is a pure antagonist of the turning caused by known dopamine D₂ agonists [56]. Here then is a

situation in which aripiprazole is a pure antagonist in a system with low dopamine tone, findings directly contradictory to the partial agonist hypothesis, but completely explicable by functional selectivity.

Another example, albeit a bit less direct, relates to Parkinson's disease (PD). Many PD patients develop psychotic side effects as a result of their use of levodopa and/or dopamine agonists (the latter largely working via D₂ receptors). By similar reasoning as espoused for schizophrenia, aripiprazole (as a partial agonist) should be very useful in treating these psychotic symptoms when added to the dopaminergic regimen of the PD patient. In fact, aripiprazole not only lacks effectiveness in treating the psychoses, it tends to worsen motor function [58].

If not a "simple" partial agonist, how does one conceptualize aripiprazole working as a functionally selective D₂ ligand. It is to be noted that aripiprazole, like the other antipsychotics, is not selective for a single target. It has high affinity for a few other receptors (e.g., 5-HT_{1A}) and modest affinity for several more [55]. Nonetheless, the interest in this compound revolves around its D₂ action. Clearly its intrinsic activity varies markedly depending on the signaling environment of the D₂ receptor [4,53,55]. It is fascinating to hypothesize how this specifically translates into functional changes in the intact organism. It may be, for example, that the cellular changes that cause post-denervation supersensitivity also change the D₂ signaling environment such that aripiprazole loses intrinsic activity. This would explain the results in the unilateral 6-OHDA rat or in PD patients. Conversely, it might be supposed that at the critical D₂ receptors in the dopamine mesolimbic terminal fields where aripiprazole is a low intrinsic activity ligand, possibly explaining the common observation that while exceptionally well-tolerated for this class of medication, the drug may be slightly less effective than compounds with pure D₂ antagonist effects.

Conclusions

The examples I have discussed hopefully will trigger ideas about how the mechanisms discussed in this issue are of pragmatic, as well as heuristic, importance. The purpose was not to prove that functional selectivity leads to novel drug action, rather that it might. A consequence of functional selectivity, at least in theory, is that it becomes possible to separate the desired versus undesired effects of a single molecule acting via a single receptor. The cartoon in Figure 2 shows how this might happen in the ideal. In the case of aripiprazole, this might be the useful antipsychotic effects versus the undesired motor side effects. Functionally selective drugs have the promise of improving the therapeutic profile of compounds acting at a wide variety of receptors.

The question, then, is how one goes about this. The answer is from all angles. Elucidation of proximal mechanisms, discussed elsewhere in this issue and in recent perspectives [4,8], is clearly of paramount importance. Knowledge of the involved mechanisms can lead to batteries of assays that may be useful in detecting compounds with functionally selective profiles. In addition, it is important to remember that drugs that are functionally selective may be considered to have both orthostatic and allosteric binding domains (i.e., while occupying aspects of the endogenous ligand's binding site, they also may extend into other regions of the receptor not normally perturbed by the endogenous ligand). As such, allosterism (see Leach et al. this issue) may be another way of invoking functional selectivity.

Molecular mechanisms aside, classic pharmacological approaches (at least for the near future) still have value for discovering drugs with novel actions in many therapeutic areas. The published history of aripiprazole provides a lesson in this regard: the compound was selected because of its effects on a battery of *in vivo* and *ex vivo* assays of purported behavioral

functional relevance. Yet it will be mechanistic studies that drive us to the next generation of drugs. For example, bifeprunox, an antipsychotic drug candidate pending approval before the US FDA., is purported to be a D₂ “partial agonist” like aripiprazole. It will be very interesting to see how functional effects and the underlying mechanisms are similar or different between these two drugs. The integration of such mechanistic data with emerging clinical and behavioral data may be very useful in determining whether the viewpoint espoused here is correct.

Acknowledgments

This work was supported, in part, by Public Health Service research grants MH073910 and MH040537.

References

1. Furchgott, RF. The use of -haloalkylamines in the differentiation of receptors and in the determination of dissociation constants of receptor-agonist complexes. In: Harper, NJ.; Simmonds, AB., editors. *Advances in Drug Research* (Vol 3 edn). Academic Press; 1966. p. 21-55.
2. Ariens EJ. Affinity and intrinsic activity in the theory of competitive inhibition. I. Problems and theory. *Arch Int Pharmacodyn Ther* 1954;99:32–49. [PubMed: 13229418]
3. Stephenson RP. A modification of receptor theory. *Br J Pharmacol* 1956;11:379–393.
4. Urban JD, et al. Functional selectivity and classical concepts of quantitative pharmacology. *J Pharmacol Exp Ther* 2007;320:1–13. [PubMed: 16803859]
5. Simmons MA. Functional selectivity, ligand-directed trafficking, conformation-specific agonism: What's in a name? *Mol Interv* 2005;5:154–157. [PubMed: 15994454]
6. Mailman, RB., et al. Functional Effects of Novel Dopamine Ligands: Dihydropyridine and Parkinson's Disease as a First Step. In: Jenner, P.; Demirdemir, R., editors. *Dopamine Receptor Subtypes: From Basic Science to Clinical Application*. IOS Stockton Press; 1998. p. 64-83.
7. Lawler, CP.; Watts, VJ.; Booth, RG.; Southerland, SB.; Mailman, RB. Society for Neuroscience Abstracts. Vol. 20. 1994. Discrete functional selectivity of drugs: OPC-14597 a selective antagonist for post-synaptic dopamine D₂ receptors; p. 525
8. Neubig RR. Missing links: Mechanisms of Protean Agonism (Relates to article by Lane, et al., Fast Forward 7 February 2007). *Mol Pharmacol*. 2007
9. Garau L, et al. Dopamine receptors: pharmacological and anatomical evidences indicate that two distinct dopamine receptor populations are present in rat striatum. *Life Sci* 1978;23:1745–1750. [PubMed: 723447]
10. Kebabian JW, Calne DB. Multiple receptors for dopamine. *Nature* 1979;277:93–96. [PubMed: 215920]
11. Neve, KA.; Neve, RL. The dopamine receptors. Neve, KA.; Neve, RL., editors. Humana Press; 1997.
12. Laduron, P. Commentary: Dopamine-sensitive adenylate cyclase as a receptor site. In: Kaiser, C.; Kebabian, JW., editors. *Dopamine Receptors*. American Chemical Society; 1983. p. 22
13. Mailman RB, Nichols DE. Dopamine D₁ receptor agonists as antiparkinson drugs. *Trends Pharmacol Sci* 1998;19:255–256. [PubMed: 9703756]
14. Mailman R, et al. Parkinson's disease and D₁ dopamine receptors. *Curr Opin Investig Drugs* 2001;2:1582–1591.
15. Bedard PJ, Boucher R. Effect of D₁ receptor stimulation in normal and MPTP monkeys. *Neurosci Lett* 1989;104:223–228. [PubMed: 2573015]
16. Elliott PJ, et al. Dopamine D₁ and D₂ receptor interactions in the MPTP-treated marmoset. *Neurosci Lett* 1992;142:1–4. [PubMed: 1357609]
17. Charifson PS, et al. Synthesis and pharmacological characterization of 1-phenyl-, 4-phenyl-, and 1-benzyl-1,2,3,4-tetrahydroisoquinolines as dopamine receptor ligands. *J Med Chem* 1988;31:1941–1946. [PubMed: 3050089]
18. Charifson PS, et al. Conformational analysis and molecular modeling of 1-phenyl-, 4-phenyl-, and 1-benzyl-1,2,3,4-tetrahydroisoquinolines as D₁ dopamine receptor ligands. *J Med Chem* 1989;32:2050–2058. [PubMed: 2527994]

19. Setler PE, et al. The central effects of a novel dopamine agonist. *Eur J Pharmacol* 1978;50:419–430. [PubMed: 568069]
20. Nichols, DE. The development of novel dopamine agonists. In: Kaiser, C.; Keabian, JW., editors. *Dopamine Receptors*. American Chemical Society; 1983. p. 201–218.
21. Mottola DM, et al. Conformational analysis of D1 dopamine receptor agonists: pharmacophore assessment and receptor mapping. *J Med Chem* 1996;39:285–296. [PubMed: 8568818]
22. Lovenberg TW, et al. Dihydropyridine, a novel selective high potency full dopamine D-1 receptor agonist. *Eur J Pharmacol* 1989;166:111–113. [PubMed: 2572425]
23. Taylor JR, et al. Dihydropyridine, a full dopamine D1 agonist, reduces MPTP-induced parkinsonism in monkeys. *Eur J Pharmacol* 1991;199:389–391. [PubMed: 1680717]
24. Brewster WK, et al. trans-10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[a]phenanthridine: a highly potent selective dopamine D1 full agonist. *J Med Chem* 1990;33:1756–1764. [PubMed: 1971308]
25. Mottola DM, et al. Dihydropyridine, a novel full efficacy D₁ dopamine receptor agonist. *J Pharmacol Exp Ther* 1992;262:383–393. [PubMed: 1352553]
26. Darney KJ Jr, et al. Behavioral effects in the rat of dihydropyridine, a high-potency, full-efficacy D1 dopamine receptor agonist. *Neuropsychopharmacology* 1991;5:187–195. [PubMed: 1684499]
27. Mottola DM, et al. Functional selectivity of dopamine receptor agonists. I. Selective activation of postsynaptic dopamine D2 receptors linked to adenylate cyclase. *J Pharmacol Exp Ther* 2002;301:1166–1178. [PubMed: 12023552]
28. Mottola DM, et al. Dihydropyridine, a selective dopamine receptor agonist that may discriminate postsynaptic D₂ receptors. *Soc Neurosci Abstr* 1991;8:18
29. Meller E, et al. Relationship between receptor occupancy and response at striatal dopamine autoreceptors. *Mol Pharmacol* 1987;31:592–598. [PubMed: 2885734]
30. Kenakin T. Drugs and receptors. An overview of the current state of knowledge. *Drugs* 1990;40:666–687. [PubMed: 2292230]
31. O'Hara CM, et al. Inhibition of dopamine synthesis by dopamine D2 and D3 but not D4 receptors. *Journal of Pharmacology & Experimental Therapeutics* 1996;277:186–192. [PubMed: 8613917]
32. Tang L, et al. Dopamine D₂ and D₃ receptors inhibit dopamine release. *J Pharmacol Exp Ther* 1994;270:475–479. [PubMed: 8071839]
33. Kilts JD, et al. Functional selectivity of dopamine receptor agonists. II. Actions of dihydropyridine in D2L receptor-transfected MN9D cells and pituitary lactotrophs. *J Pharmacol Exp Ther* 2002;301:1179–1189. [PubMed: 12023553]
34. Urban JD, et al. Aripiprazole has Functionally Selective Actions at Dopamine D(2) Receptor-Mediated Signaling Pathways. *Neuropsychopharmacology* 2007;32:67–77. [PubMed: 16554739]
35. Mailman, RB., et al. Molecular Drug Design and Dopamine Receptors. In: Neve, KA.; Neve, RL., editors. *The Dopamine Receptors*. Humana Press; 1997. p. 105–133.
36. Gay EA, et al. Functional selectivity of D2 receptor ligands in a Chinese hamster ovary hD2L cell line: evidence for induction of ligand-specific receptor states. *Mol Pharmacol* 2004;66:97–105. [PubMed: 15213300]
37. Eden RJ, et al. Preclinical pharmacology of ropinirole (SK&F 101468-A) a novel dopamine D2 agonist. *Pharmacol Biochem Behav* 1991;38:147–154. [PubMed: 1673248]
38. Smith HP, et al. Locomotor inhibition, yawning and vacuous chewing induced by a novel dopamine D2 post-synaptic receptor agonist. *Eur J Pharmacol* 1997;323:27–36. [PubMed: 9105873]
39. Delay J, et al. Therapeutic method derived from hiberno-therapy in excitation and agitation states. *Ann Med Psychol (Paris)* 1952;110:267–273. [PubMed: 13008201]
40. Carlsson A, Lindqvist M. Effect of chlorpromazine and haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol Toxicol (Copenh)* 1963;20:140–144. [PubMed: 14060771]
41. Creese I, et al. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* 1976;192:481–483. [PubMed: 3854]
42. Tamminga CA, Carlsson A. Partial dopamine agonists and dopaminergic stabilizers, in the treatment of psychosis. *Curr Drug Targets CNS Neurol Disord* 2002;1:141–147. [PubMed: 12769623]

43. Tamminga CA, et al. Schizophrenic symptoms improve with apomorphine. *Science* 1978;200:567–568. [PubMed: 347574]
44. Corsini GU, et al. The use of dopamine agonists in the treatment of schizophrenia. *Neuropharmacology* 1981;20:1309–1313. [PubMed: 7033816]
45. Smith RC, et al. Effect of apomorphine on schizophrenic symptoms. *J Neural Transm* 1977;40:171–176. [PubMed: 323423]
46. Tamminga CA, et al. Dopamine agonist treatment of schizophrenia with N-propylnorapomorphine 3. *Arch Gen Psychiatry* 1986;43:398–402. [PubMed: 2869745]
47. Kenakin, TP. Pharmacologic analysis of drug-receptor interaction. Lippincott-Raven Publishers; 1997.
48. Lahti AC, et al. Antipsychotic properties of the partial dopamine agonist (-)-3-(3-hydroxyphenyl)-N-n-propylpiperidine(preclamol) in schizophrenia. *Biol Psychiatry* 1998;43:2–11. [PubMed: 9442338]
49. Tamminga CA, et al. Pharmacologic properties of (-)-3PPP (preclamol) in man. *J Neural Transm Gen Sect* 1992;88:165–175. [PubMed: 1358119]
50. Tamminga CA. Partial dopamine agonists in the treatment of psychosis. *J Neural Transm* 2002;109:411–420. [PubMed: 11956961]
51. Stahl SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part 1, “Goldilocks” actions at dopamine receptors. *J Clin Psychiatry* 2001;62:841–842. [PubMed: 11775041]
52. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. *CNS Drugs* 2004;18:251–267. [PubMed: 15015905]
53. Lawler CP, et al. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. *Neuropsychopharmacology* 1999;20:612–627. [PubMed: 10327430]
54. Burris KD, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther* 2002;302:381–389. [PubMed: 12065741]
55. Shapiro DA, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology* 2003;28:1400–1411. [PubMed: 12784105]
56. Kikuchi T, et al. 7-(4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2(1H)-quinolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and postsynaptic D2 receptor antagonistic activity. *J Pharmacol Exp Ther* 1995;274:329–336. [PubMed: 7616416]
57. Ungerstedt U, Arbuthnott GW. Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. *Brain Res* 1970;24:485–493. [PubMed: 5494536]
58. Friedman JH, et al. Open-label flexible-dose pilot study to evaluate the safety and tolerability of aripiprazole in patients with psychosis associated with Parkinson's disease. *Mov Disord* 2006;21:2078–2081. [PubMed: 17013906]

Abbreviations

3-PPP	Preclamol; (-)-3-(3-hydroxyphenyl)-N-n-propylpiperidine
6-OHDA	6-hydroxydopamine; 1,2,4-trihydroxy-5-(2-aminoethyl)benzene
Dihydropyridine	<i>trans</i> -10,11-dihydroxy-5,6,6a,7,8,12b-hexahydrobenzo[<i>a</i>]phenanthridine
PD	Parkinson's disease
propylDHX	N-n-propyldihydropyridine; (±)- <i>trans</i> -6-propyl-10, 11-dihydroxy-5,6,6a, 7,8,12b-hexahydrobenzo[<i>a</i>]phenanthridine

Figure 1.

Ligand-receptor interactions can cause functional selectivity that is expressed in several ways. The potency of ligands can be differentially affected when two different receptor-mediated assays are conducted in the same cell line (left panel). The relative potency of aripiprazole in two functional assays differs by more than two orders of magnitude, unlike dopamine or other dopamine agonists. In addition, a ligand may cause discrete differences in intrinsic activity (right side). PropylDHX is a full agonist at D_{2L} mediated inhibition of adenylate cyclase (top right panel), yet is an antagonist at D_{2L} -mediated inhibition of dopamine release (bottom right panel). Conversely, quinpirole affects both functions similarly. Data originally from Kilts et al. [33] and Urban et al. [34]

Figure 2.

How a functionally selective drug might decrease side effects. In this hypothetical example, effects on GIRK channels are linked to a side effect, whereas effects on adenylate cyclase are linked to therapeutic effects. The functionally selective drug (left panel) has actions primarily on adenylate cyclase, whereas the typical agonist (right panel) has effects on both pathways. Thus, the functionally selective drug would have a better therapeutic index. This cartoon shows the polar extremes (pure agonism vs pure antagonism for the functionally selective drugs). In practice, a useful functionally selective ligand might have different degrees of partial intrinsic activity (not resulting from differences in receptor reserve!) at two (or more) key transduction mechanisms.