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Dopamine receptor signaling and current and future antipsychotic drugs

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Abstract

All currently efficacious antipsychotic drugs have as part of their mechanism the ability to attenuate some or all of their signaling through the dopamine D₂ receptor. More recently, the dopamine D₁ receptor has been hypothesized to be a promising target for the treatment of negative and/or cognitive aspects of schizophrenia that are not improved by current antipsychotics. Although cAMP has been presumed to be the primary messenger for signaling through the dopamine receptors, the last decade has unveiled a complexity that has provided exciting avenues for the future discovery of antipsychotic drugs (APDs). We review the signaling mechanisms of currently approved APDs at dopamine D₂ receptors, and note that aripiprazole is a compound that is clearly differentiated from other approved drugs. Although aripiprazole has been postulated to cause dopamine stabilization due to its partial D₂ agonist properties, a body of literature suggests that an alternate mechanism, functional selectivity, is of primary importance. Finally, we review the signaling at dopamine D₁ receptors, and the idea that drugs that activate D₁ receptors may have use as APDs for improving negative and cognitive symptoms. We address the current state of drug discovery in the D₁ area, and its relationship to novel signaling mechanisms. Our conclusion is that although the first APD targeting dopamine receptors was discovered more than a half-century ago, recent research advances offer the possibility that novel and/or improved drugs will emerge in the next decade.

Keywords

Dopamine; schizophrenia; antipsychotic drug; functional selectivity; drug discovery

1. Introduction

Dopamine plays a role in numerous biological processes, making it unsurprising that many drugs target dopamine receptors. Although dopamine neurons are relatively scarce in the brain, their importance is highlighted by the number of normal brain processes (e.g., memory, motor behavior, and reward) and diseases that are modulated by dopamine receptor signaling. For example, the loss of dopamine neurons in the substantia nigra results in

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Parkinson's disease, whereas hyperactive dopaminergic signaling is believed to be a major factor in the positive symptoms of schizophrenia. Since the serendipitous discovery of the antipsychotic drug (APD) chlorpromazine over 50 years ago, many advances have been made in the understanding of dopamine structure and signaling. After 50 years of schizophrenia drug development, however, the efficacy of APDs has not significantly improved, although therapeutic indices are somewhat better because of a reduction in many side effects. Although positive symptoms of schizophrenia can be treated effectively by current drugs, negative symptoms and cognitive defects are much less responsive to current drugs. Thus, there is clearly a need for novel therapies. Drugs that activate D₁-mediated signaling pathways may alleviate the negative symptoms and cognitive deficits and decrease some of the side effects of current APDs. Because the mechanisms of many APDs are not completely understood, understanding how different dopamine signaling pathways play a role in the actions of APDs will be one critical direction for the design of novel treatments. This chapter will provide an overview of the current state of research in these areas.

1.1. Background on Dopamine Receptors

Dopamine receptors are members of the G protein-coupled receptor (GPCR) superfamily. There are five dopamine receptor genes that produce six distinct dopamine receptors in humans. Dopamine receptors were initially divided into two pharmacological families based on their ligand recognition properties and their effects on cAMP production: the D₁-like receptors and the D₂-like receptors (Garau et al., 1978; Kebabian and Calne, 1979). The D₁-like receptors consist of the D₁ and D₅ dopamine subtypes, whereas the D₂-like receptors include two major splice variants of the D₂ receptor [D_{2L} (long), and D_{2S} (short)] plus the D₃ and D₄ receptors. There are also splice variants for the D₃ (Giros et al., 1989; Sokoloff et al., 1990) and D₄ (O'Malley et al., 1992; van Tol et al., 1991) receptors, but the effects of these variants on behavioral phenotypes have been controversial (Jonsson et al., 2001; Jonsson et al., 2002; Kotler et al., 2000; Mill et al., 2001; Schmidt et al., 2001; Swanson et al., 1998). No splice variants exist for the D₁-like receptors because their genes are intronless. The D₁-like receptors activate G_{αs/olf} and stimulate cAMP production, whereas the D₂-like receptors activate G_{αi/o} to inhibit adenylate cyclase activity and cAMP production. There are also differences in the localization of the dopamine receptors. The D₁-like receptors are predominately found postsynaptically (Levey et al., 1993), whereas the D₂-like receptors are found postsynaptically on dopaminergic target neurons (Levey et al., 1993; Sesack et al., 1994) and as presynaptic and autoreceptors on dopamine neurons (L'hirondel et al., 1998; Mercuri et al., 1997). Although several subtypes of dopamine receptors may co-localize on some cells (Surmeier et al., 1996), the receptors are often largely segregated (Gerfen et al., 1990; Le Moine and Bloch, 1995).

There are three major brain dopamine pathways that are involved in brain actions: the nigrostriatal (from cells in the A9 region), the mesolimbic-cortical (from cells in the A10 or ventral tegmentum), and the tuberoinfundibular (hypothalamic) system (Ungerstedt, 1971). In addition, peripheral dopamine neurons are involved in important physiological functions, such as renal and cardiovascular functions and immune regulation. Given that dopamine is involved in both central nervous system (CNS) and peripheral functions, it is not surprising

that alterations in dopaminergic signaling are related to numerous diseases and disorders, such as Parkinson's disease, schizophrenia, depression, dyskinesias, and hypertension.

1.2. Dopamine Receptors and Antipsychotic Drug Action

Dopaminergic signaling is critical for a variety of functions, and abnormal dopaminergic signaling is involved in a variety of CNS disorders. Early studies demonstrated that dopamine and its receptors play a role in the therapy or etiology of psychiatric and neurological disorders (Carlsson, 1964; Carlsson and Lindqvist, 1963; Carlsson et al., 1957; Creese et al., 1976; Ehringer and Hornykiewicz, 1960). For motor function, the localization of dopamine receptors in the two principal striatal outflow pathways was shown to affect their role in neurological diseases (Albin et al., 1989; DeLong, 1990; Gerfen, 2000a; Gerfen, 2000b; Graybiel, 1990; Robertson et al., 1992; Starr, 1995). D₁ receptors are expressed on striatal GABAergic medium spiny neurons (MSNs) that project to the medial globus pallidus and the substantia nigra pars reticulata (i.e., the direct nigrostriatal pathway), whereas D₂ receptors are expressed on MSNs that project to the lateral globus pallidus (i.e., the indirect pathway).

In schizophrenia, antidopaminergic drugs have been used clinically for more than 50 years, yet many mechanisms of dopaminergic drug actions remain unknown. The classical dopamine hypothesis postulated that the positive symptoms of schizophrenia were a response to hyperactive dopaminergic signaling, a hypothesis that was supported by the ability of APDs to block D₂ receptors and the psychotic effects induced by dopaminergic drugs (Carlsson and Lindqvist, 1963; Creese et al., 1976; Seeman et al., 1975; Seeman and Lee, 1975). Based on this early data, much of the effort in APD development has been focused on antagonizing D₂ receptors. Although D₁ and D₂ receptors are generally not found on the same neurons, the activation of D₁ receptors can enhance the stereotyped and motor D₂-mediated behavioral responses (LaHoste et al., 2000; Mailman et al., 1984; Martin-Iverson and Yamada, 1992; White et al., 1988). In addition, both D₁ and D₂ receptors are involved in learning and memory (Goldman-Rakic et al., 2004). Dopamine D₁ and D₂ receptors signal through G α subunits with opposing effects; however, they often signal through the same $\beta\gamma$ subunits, suggesting that $\beta\gamma$ signaling may mediate some of the interactions between these receptors. The interactions between D₁ and D₂ receptors may play an important role in schizophrenia and the design of novel APDs to treat all of the symptoms of schizophrenia. Selective D₁ receptor antagonists have not shown efficacy in treating schizophrenia, and may actually exacerbate extrapyramidal side effects and tardive dyskinesia (Den Boer et al., 1995; Karle et al., 1995; Karlsson et al., 1995). Conversely, all currently approved antipsychotics have actions at dopamine D₂ receptors, suggesting this is an important, if not obligatory, aspect of efficacy against positive symptoms (Miyamoto et al., 2000). As will be discussed below, the combination of a D₁ agonist and D₂ antagonist/ functionally selective drug may be one route to next generation therapy.

1.3. Dopamine Receptors and Functional Selectivity

The first evidence for a biochemical mechanism of dopamine systems was the observation that dopamine could dose-dependently stimulate the synthesis of the second messenger cAMP (Kebabian et al., 1972), and this activation of cAMP was antagonized by

antipsychotic drugs (Clement-Cormier et al., 1974) in proportion to the clinical potency of the drugs (Clement-Cormier et al., 1974; Iversen, 1975). For many years, the primary focus of drug discovery efforts was on the regional and cellular localization of different dopamine receptors and how subtype-selective drugs might be useful in schizophrenia and other CNS disorders. The common assumption was that drug effects on dopamine receptor-mediated cAMP signaling would be predictive of clinical action (see reviews, e.g., Beaulieu and Gainetdinov, 2011; Huang et al., 2001; Mailman, 2007). Thus, the development of novel antipsychotic drugs focused on several areas: 1) non-dopamine receptor targets; 2) dopamine isoform-selective antagonists; 3) multi-targeted ligands (“magic shotguns”); and/or 4) selective presynaptic dopamine agonists (Roth et al., 2004). A drug that worked via any of these mechanisms usually would be assessed preclinically by its biochemical actions on receptor-mediated cAMP synthesis. The accepted concept in all such discovery research was that a drug would have a property called “intrinsic efficacy” that could be assessed by its action at any signaling pathway of the targeted receptor. Thus, classical pharmacology posited that a ligand either acts as an agonist, partial agonist, antagonist, or inverse agonist (i.e., its intrinsic efficacy); and a drug would always cause the same type of functional change, although this could be quantitatively affected by factors such as receptor reserve and strength of signaling.

Although dopamine receptors were originally classified based on their effects on cAMP synthesis, it became clear that signaling through modulation of adenylate cyclases is only a fraction of how dopamine receptors modulate cellular function. Many recent reviews have covered the signaling mechanisms of dopamine receptors (Beaulieu and Gainetdinov, 2011; Mailman and Huang, 2007; Neve et al., 2004). Dopamine receptor signaling is now widely appreciated to be more complex than simply changes in cAMP levels. Recent studies have shown that dopamine receptors may even signal through G protein-independent pathways such as those involving β -arrestin (Beaulieu et al., 2007a). With this awareness of the complexity of mechanisms of signaling, there is also mounting evidence that some drugs can cause markedly different responses at the signaling cascades mediated by a single receptor isoform. This remarkable departure from classical pharmacological dogma has been referred to by many names, but the most commonly used term is “functional selectivity” (Urban et al., 2007a).

The term “functional selectivity” was first used to describe findings with the antipsychotic drug aripiprazole (Lawler et al., 1994) and with experimental dopamine agonists (Mailman et al., 1998). Essentially, functional selectivity means that a drug may have different actions at different signaling pathways mediated by the same receptor (e.g., a ligand could be an agonist at one pathway and an antagonist at another), and these differences are not explicable by classical concepts, such as receptor reserve or strength of signaling. A consequence of this idea is that assigning a specific type of intrinsic efficacy (*vide supra*, a constant inherent property of a drug) to a drug may not be valid. Thus, drugs that are functionally selective will have different intrinsic activity (agonist, partial agonist, antagonist, or inverse agonist) in two or more different assay systems after accounting for factors such as receptor reserve. This places particular importance on the milieu in which a drug is characterized (e.g., the cell or tissue being studied, the signaling pathway being

assessed, and/or the degree of receptor expression). We recently provided an overview of the molecular mechanisms that may influence the functional selectivity of a variety of GPCRs (Urban et al., 2007a); many of the mechanisms are relevant to dopamine receptors.

Upon reflection, it should not be surprising that functional selectivity exists. GPCRs can couple with multiple G proteins and signal through G protein-independent mechanisms, such as β -arrestins. Moreover, the presence of various kinases, phosphatases, and other signaling molecules [e.g., G protein-coupled receptor kinases (GRKs) and regulators of G protein signaling (RGS) proteins] are dependent on cellular localization and can influence signaling. In addition, dopamine receptor signaling can vary in different brain regions depending on the expression patterns of GRKs, β -arrestins, and other signaling molecules. For example, RGS proteins can affect ligand actions and signaling by negatively modulating G protein signaling, and RGS proteins may be particularly important for D₂ signaling because they enhance GTP hydrolysis through G $\alpha_{i/o}$ but not G α_s . As if the signaling mechanisms are not already complicated enough, dopamine receptors and other GPCRs can form homodimers as well as heterodimers with receptors from other superfamilies, and these receptor complexes may result in significant pharmacological changes. For functional considerations, we must consider the interaction of drugs with receptor-based signaling complexes, sometimes called the “signalsome” (Mercurio et al., 1997; Wang and Malbon, 2011), rather than the receptor alone (Urban et al., 2007a) because different ligands induce or stabilize different receptor conformational states that influence which signaling pathways are activated by the receptor. Understanding the signaling molecules that are important for specific functions will be critical for the development of functionally selective drugs.

Rather than simply targeting specific receptor isoforms, taking advantage of the functionally selective nature of novel ligands could, in theory, allow for greater control over the effects of drugs. For example, drugs could be designed that selectively activate the signaling pathways that are responsible for the therapeutic effects of a drug without stimulating pathways that are involved in side effects. With the exciting possibilities of functionally selective ligands, however, comes a greater importance for understanding receptor structure, dynamics, and signal transduction. Using APDs as an example, understanding all of the signaling mechanisms of clinically used APDs and the signaling pathways responsible for drug effects and disease manifestation will provide invaluable knowledge for the development of novel therapeutics.

1.4. Allosteric Targeting of Dopamine Receptors

Recently, the idea of allosteric ligands for GPCRs has been an important arena of investigation because of the potential of allosteric ligands to have actions (Conn et al., 2009; Jakubik et al., 1996). Although no allosteric ligands have not yet been conclusively demonstrated for dopamine receptors, this is likely to become important in the future. The conservation in the ligand binding domains of the dopamine receptor family sometimes has created difficulties in discovering ligands with adequate pharmacological selectivity (e.g., D₁ vs. D₅). This problem could be overcome if less conserved aspects of the receptor could be targeted. Second, allosteric ligands can theoretically have actions far more diverse than orthosteric ligands. Indeed, allosteric ligands could cause conformational changes that

directly activate the receptor (allosteric agonist) or conformational changes that block the actions of orthosteric ligands (allosteric antagonist). In addition to these direct actions on receptor function, allosteric ligands could have modulatory functions via interactions with orthosteric ligands, either synergizing (positive allosteric modulation) or attenuating (negative allosteric modulation) the actions of the endogenous ligand. In theory, allosteric ligands offer the potential for fine-tuning cellular signaling, especially in situations where the discovery of orthosteric ligands has been unsuccessful, and there are now examples that allosteric targeting can lead to an approved drug for a GPCR (e.g., cinacalcet; Block et al., 2004). These possibilities may be useful for both D₁ and D₂ receptors as it relates to aspects of the treatment of schizophrenia. As noted earlier, there is no ligand yet identified for any of the dopamine receptors that is a clear allosteric ligand, but there has been some suggestion that this may be possible (Agnati et al., 2006; Huber et al., 2012).

2. D₂-like signaling

A major mediator of D₂-like signaling (i.e., D₂, D₃, and D₄ receptors) is the G $\alpha_{i/o}$ class of G proteins, which are inactivated by pertussis toxin-catalyzed ADP-ribosylation (Bokoch et al., 1983; Kurose et al., 1983). The G $\alpha_{i/o}$ class of G proteins inhibits adenylate cyclase and cAMP accumulation (De Camilli et al., 1979; Stoof and Kebabian, 1981). Interestingly, studies have shown that D₂-like inhibition of adenylate cyclase can lead to presynaptic/autoreceptor decreases in tyrosine hydroxylase activity and decreased firing of nigrostriatal dopamine neurons. The two isoforms of D₂ receptors [i.e., D_{2Long} (D_{2L}) and D_{2Short} (D_{2S})] appear to activate multiple G $\alpha_{i/o}$ subtypes, but the G α_o subtype is the subtype that is most robustly activated by both D_{2L} and D_{2S} (Jiang et al., 2001). Both D₂ and D₄ receptors inhibit adenylate cyclase in most clonal and *in situ* cells (Huff, 1997; Oak et al., 2000); however, inhibition of adenylate cyclase by D₃ receptors is usually undetectable without molecular manipulation. Interestingly, D₃ dopamine receptors tend to bind agonists with higher affinity than the other D₂-like receptors. In addition, D₃ dopamine receptors bind agonists in a GTP-insensitive manner (Sokoloff et al., 1992), which has been hypothesized to be because of a receptor conformation with high affinity for agonists regardless of interactions with G proteins (Vanhauwe et al., 2000).

Although D₂ receptors are a target of all APDs, differences in the therapeutic profiles of APDs are influenced by interactions with other receptors and differential activation of D₂-mediated signaling pathways. In addition to D₂-like receptor signaling through adenylate cyclase, D₂-like receptors modulate many other signaling pathways, including phospholipases, ion channels, mitogen activated protein (MAP) kinases, and the Na⁺/H⁺ exchanger (Huff et al., 1998). Moreover, the dissociation of G $\beta\gamma$ subunits following D₂ receptor activation has significant effects on K⁺ currents, and D₂ receptor-mediated increases in K⁺ currents decrease cell excitability. D₂-like receptors activate a G protein-regulated inwardly rectifying potassium channel (GIRK or Kir3), which modulates several potassium currents in various tissues (Greif et al., 1995; Lacey et al., 1987; Liu et al., 1994; Oxford and Wagoner, 1989). In addition, dopamine release-regulating autoreceptors are coupled to potassium channels (Cass and Zahniser, 1991) rather than inhibition of adenylate cyclase (Memo et al., 1986), and there is robust regulation of GIRK currents by D₂ receptors in substantia nigra dopamine neurons (Davila et al., 2003).

D₂-like receptors can also regulate Na⁺ channels and L, N, and P/Q-type Ca²⁺ channels, and the regulation of these ion channels may involve Gβγ actions (Kuzhikandathil and Oxford, 1999; Lledo et al., 1992; Okada et al., 2003; Seabrook et al., 1994a; Seabrook et al., 1994b; Surmeier and Kitai, 1993; Yan et al., 1997; Zamponi and Snutch, 1998). Interestingly, D₂-like receptor stimulation can either increase or decrease Na⁺ currents depending on the subtype of D₂-like receptors that are expressed by a given cell (Surmeier et al., 1992; Surmeier and Kitai, 1993). In most D₂ agonist-responsive neurons, however, D₂-like receptor stimulation decreases Na⁺ currents. In addition, D₂-like receptor signaling tends to inhibit Ca²⁺ channel activity. Moreover, D₂-like receptor signaling can regulate neurotransmitter release via N-type Ca²⁺ channels (Dunlap et al., 1995; Koga and Momiyama, 2000; Svensson et al., 2003). Agonist effects at heterologously expressed D₂, D₃, or D₄ receptors can also activate the widely expressed Na⁺/H⁺ exchanger NHE1 (Neve et al., 2004).

D₂ receptor activation has also been shown to stimulate MAP kinases, including the two isozymes of extracellular signal-regulated kinase (ERK) (Choi et al., 1999; Ghahremani et al., 2000; Huff, 1996; Kim et al., 2004; Luo et al., 1998; Oak et al., 2001; Voyno-Yasenetskaya et al., 1994; Welsh et al., 1998) and stress-activated protein kinase/Jun amino-terminal kinase (SAPK/JNK) (Luo et al., 1998). In addition, D₂ and D₄ receptors can potentiate arachidonic acid release induced by calcium-mobilizing receptors both directly and through cytosolic phospholipase A2 (Chio et al., 1994; Kanterman et al., 1991; Piomelli et al., 1991; Vial and Piomelli, 1995). Arachidonic acid and its lipoxygenase and cyclooxygenase metabolites have numerous effects on cellular function, including feedback regulation of D₂-like signaling and dopamine transport (DiMarzo and Piomelli, 1992; L'hirondel et al., 1995; Piomelli and Greengard, 1990; Zhang and Reith, 1996). Interestingly, D₂ receptors can also stimulate phospholipase D, which catalyzes the hydrolysis of phosphatidylcholine to form choline and phosphatidic acid (Mitchell et al., 1998; Senogles, 2000).

Dopamine D₂ receptor activation can also result in G protein-independent signaling, such as direct interactions with ion channels (e.g., NMDA) and signaling through GRKs and arrestins. Importantly, the GRK/arrestin pathway can both suppress G protein signaling and promote G protein-independent signaling. Although differential effects can occur based on the cellular expression of GRKs and arrestins, most evidence of G protein-independent signaling relates to the role of β-arrestin 2. β-arrestin 2 is a key member of the GPCR desensitization machinery that is involved in dopamine signaling through protein kinase B (Akt) and glycogen synthase kinase 3 (GSK3) (Beaulieu et al., 2008; Beaulieu et al., 2007b). Indeed, GRK phosphorylation of dopamine receptors leads to the recruitment and binding of β-arrestins, which prevents G-protein-dependent signaling even if an agonist is still present. The majority of the evidence is based on studies using a variety of genetically altered mice that were deficient in major constituents of GPCR signaling, including GRKs, β-arrestins, dopamine transporter (DAT), and Akt. Mechanistically, the time course of β-arrestin/Akt signaling at the D₂ receptor takes much longer to develop (hours versus minutes) compared with the G protein-mediated cAMP/PKA response (Beaulieu et al., 2005; Beaulieu et al., 2004; Beaulieu et al., 2007b). Thus, drugs that alter D₂ receptor signaling (e.g., APDs) may result in opposing responses following drug administration. For example, the initial response

would be a rapid G protein (i.e., cAMP) mediated response that could be desensitized, whereas delayed responses (e.g., β -arrestin-mediated) might last for a longer period of time and may not be able to be desensitized. The slow response of the β -arrestin/Akt pathway may be indicative of its downstream effects on gene transcription, which can alter target protein transcriptional profiles and chromatin remodeling (Alimohamad et al., 2005; Beaulieu and Caron, 2005; Kang et al., 2005; Li et al., 2007). Although it is tempting to speculate that the β -arrestin/Akt pathway is the one primarily involved in clinical response to antipsychotic drugs, it is unlikely that the answer will be so simple.

2.1. Evidence for Functional Selectivity at D₂-Like Receptors

2.1.1. Hypothesized Presynaptic/Autoreceptor Selective Ligands and Functional Selectivity—Dopamine D₂ receptors have been studied as a drug target for more than 50 years, and D₂ ligands have been used for schizophrenia, Parkinson's disease, and a variety of other psychiatric and neurological conditions. One of the major driving forces for the search for D₂ drugs was the “dopamine hypothesis of schizophrenia”, which posits that excess dopamine release and/or excess sensitivity of dopamine-receptive neurons was the cause of what are now called positive symptoms. Interestingly, this hypothesis is highly relevant to the discovery and validation of the functional selectivity of dopamine receptor ligands. The classical APDs were D₂ antagonists, and antagonism of D₂ receptors has been accepted as a way of controlling the positive symptoms of schizophrenia (Creese et al., 1976). Interestingly, activation of dopamine autoreceptors, which are primarily D₂ receptors and some D₃ receptors, causes a decrease in both the synthesis and the release of dopamine and a decrease in the firing of dopamine neurons. Interestingly, both dopamine and D₂ agonists tend to have higher potency at the effects mediated by the autoreceptors compared with the postsynaptic D₂ functions (Feenstra et al., 1983). These important findings explain why the behavioral response to a full D₂ agonist is typically biphasic with respect to dose: the inhibition seen at low doses is the result of autoreceptor stimulation, and the stimulation at higher doses is the result of direct postsynaptic activation. One of the major mechanisms explaining this biphasic effect is greater presynaptic D₂-like receptor reserve (Meller et al., 1987).

Pharmacological theory suggests that high receptor reserve in the D₂ presynaptic receptors would make partial agonists much more efficacious (Kenakin, 1997); thus, researchers suggested the use of D₂ partial agonists as APDs. Data from *in vitro* and animal studies suggested that the partial agonist (–)3-PPP (preclamol) might be an excellent candidate. Because studies had shown that low doses of agonists selectively activate D₂ autoreceptors and activation of D₂ autoreceptors inhibits dopamine release and postsynaptic activation, another treatment strategy was to use a low dose of a full agonist. Although both mechanisms have a good theoretical basis, the early clinical data were disappointing (Corsini et al., 1981; Lahti et al., 1998; Smith et al., 1977; Tamminga et al., 1992; Tamminga et al., 1986; Tamminga et al., 1978). In retrospect, this was probably not unexpected because of issues in achieving the “right” presynaptic relative receptor occupancy without temporal fluctuations or finding a partial agonist with just the “right” intrinsic activity. Nevertheless, the “partial agonist hypothesis” was revived when

aripiprazole was shown to have clinical efficacy. The difference between aripiprazole and several earlier drugs, however, is that aripiprazole is a functionally selective drug.

2.1.2. Early Evidence for the Functional Selectivity of Dopaminergic

Compounds—To the best of our knowledge, the first clear example of dopamine receptor functional selectivity resulted from serendipitous findings with dihydrexidine (DHX). Dihydrexidine was designed to be a selective D₁ agonist, but studies showed that it also had D₂ affinity (Brewster et al., 1990; Mottola et al., 1992). An examination of the functional characteristics of DHX and a more D₂-selective analog (N-n-propyldihydrexidine; PrDHX) showed that both compounds competed for D₂ receptors in heterologous systems and in brain tissue with shallow, guanine-nucleotide-sensitive curves that were similar to typical agonists (Kilts et al., 2002; Mottola et al., 1992; Mottola et al., 2002). We also examined the functional effects of these compounds in many *in vitro* systems, and both compounds had full intrinsic activity at inhibiting adenylate cyclase activity, which could be blocked by D₂ antagonists (Kilts et al., 2002; Mottola et al., 2002). The compounds also inhibited prolactin secretion *in vivo*. Although the functional studies predicted that both DHX and PrDHX were full agonists, neither ligand activated D₂-like presynaptic autoreceptors, which mediate inhibition of dopamine neuron firing, dopamine release, and dopamine synthesis (Kilts et al., 2002; Mottola et al., 2002). In addition, *in vivo* experiments showed that DHX was an antagonist of the physiological actions of the potent D₂ agonist apomorphine (Mottola et al., 2002). Although the *in vitro* functional characterization suggested that DHX had both D₁ and D₂ agonist properties, its behavioral effects were different from apomorphine or amphetamine. Interestingly, the behavioral effects of DHX appeared to be primarily D₁-like, even at very high doses (Darney, Jr. et al., 1991).

These early *in vitro/in situ* data suggested that DHX and PrDHX had high intrinsic activity at postsynaptic D₂-like receptors but low intrinsic activity at presynaptic receptors (Mottola et al., 1991). Off-site actions were largely excluded by both receptor screening and competitive pharmacological studies (Mottola et al., 1992). Although a D₄ contribution could be ruled out based on localization, it was possible that DHX and PrDHX were agonists at one dopamine receptor isoform (e.g., D_{2L}) but antagonists at another (e.g., D_{2S} or D₃). Interestingly, studies showed that DHX and PrDHX were agonists at D_{2L} receptors for the cAMP pathway, whereas they were antagonists at presynaptic autoreceptor functions. Taken together, these studies led to the hypothesis that DHX and PrDHX were D₂ functionally selective (Mottola et al., 1991).

Following the discovery and initial characterization of DHX, its functional selectivity was demonstrated in several model systems. For example, DHX was a full agonist at inhibiting adenylate cyclase in pituitary lactotrophs, and this activity was blocked by D₂ antagonists but not D₁ antagonists. In addition, DHX had little intrinsic activity at D₂ receptors coupled to G_{IRK} and was an antagonist at D₂ autoreceptors (Mottola et al., 2002). One advantage of the lactotrophs was that they only express products of the D₂ gene (DRD2; Bouthenet et al., 1991). We also examined the effects of DHX and PrDHX in mesencephalic-derived MN9D cells, where the transfection of the D_{2L} receptor has been shown to cause inhibition of adenylate cyclase and inhibition of dopamine release that is similar to dopamine neurons (O'Hara et al., 1996; Tang et al., 1994). Neither DHX nor PrDHX had effects in

untransfected MN9D cells, but after D_{2L} transfection, both compounds (as well as the reference D₂ agonist quinpirole) were full agonists at inhibition of adenylate cyclase activity. Importantly, these agonist effects were blocked by D₂, but not D₁, antagonists. Although quinpirole caused a concentration-dependent, reversible depolarization-induced release of dopamine, neither DHX nor PrDHX inhibited dopamine release. Moreover, PrDHX actually antagonized the effects of quinpirole (Kilts et al., 2002). Taken together, these studies convinced us that functional selectivity was real.

The concept of functional selectivity was initially met with resistance because classical pharmacological theory did not allow for a molecule to be both a full agonist and pure antagonist at the same receptor (i.e., not having consistent intrinsic efficacy) (Stephenson, 1956); however, studies had shown that GPCRs could have effects via different signaling partners (Kenakin, 1990). Although the common theoretical conceptualizations of receptors was in the form of discrete active states (De Lean et al., 1980; Leff et al., 1997), our conceptualization was of a dynamic system in which ligands could induce an essentially limitless number of conformational states of a target receptor, which could cause markedly different effects on receptor signaling partners (Mailman and Gay, 2004; Mailman et al., 1997). Indeed, functional selectivity has sometimes been explained as the stabilization of novel discrete active states of a receptor. Our concept was that functionally selective ligands induce unique conformational states of a receptor that are distinct from those caused by either the endogenous ligand or by antagonists. In a sense, binding of the ligand provides the driving force needed for the receptor to assume conformations that would otherwise not be energetically favorable. Understanding the molecular mechanisms that mediate functional selectivity and the impacts on drug action *in vivo* are critical.

2.1.3. Functional Selectivity in Vitro Affects Pharmacological Effects in Vivo—

Because the concept of functional selectivity was initially met with such resistance, studies demonstrating the relevance of functional selectivity to drug actions *in vivo* were necessary. Studies with dihydrexidine did not show the typical behavioral actions of a D₁:D₂ agonist (Darney, Jr. et al., 1991), but this may be because the D₁ selectivity masked the D₂ effects. To avoid this issue, studies also examined PrDHX, which is much more D₂:D₁ selective (similar to apomorphine). Importantly, PrDHX showed full intrinsic activity at D₂-mediated inhibition of adenylate cyclase. Although classic pharmacology would have predicted that a compound with full intrinsic activity at D₂-mediated adenylate cyclase would have behavioral effects similar to apomorphine or the prototypical D₂ agonist quinpirole (i.e., locomotor inhibition at low doses and locomotor stimulation at higher doses) (Eden et al., 1991), PrDHX only caused modest locomotor inhibition across a wide range of doses, and there were no competing behaviors that might have interfered with locomotion (Smith et al., 1997). This provided the first evidence that functionally selective compounds would have novel pharmacological actions. The potential impact of a functionally selective ligand is illustrated in Figure 1. In theory, a ligand should be able to discriminate between canonical functions mediated by different G protein heterotrimers and differentially affect long-term drug responses.

2.1.4. D₂ Functionally Selective Drugs and Schizophrenia—Chlorpromazine was serendipitously discovered approximately 60 years ago (Delay et al., 1952), and scientists soon realized that the antipsychotic effects were due to antidopaminergic actions (Carlsson and Lindqvist, 1963), which were later shown to result from blockade of D₂ dopamine receptors (Creese et al., 1976). Although non-dopaminergic drugs are being tested, all current APDs have some degree of D₂ antagonism as part of their pharmacological profile. Classical APDs, however, elicit numerous side effects, and researchers are constantly searching for improved APDs. One of the novel hypotheses of interest to the field was that drugs with dopamine agonist properties might decrease dopamine neurotransmission and have dopamine antagonist-like effects (Tamminga and Carlsson, 2002). Indeed, a high-affinity partial dopamine agonist that activated presynaptic D₂ autoreceptors and had low intrinsic activity at postsynaptic D₂ receptors could reduce dopamine neurotransmission. One of the most recently approved APDs, aripiprazole, was touted as the first high affinity, low intrinsic activity partial D₂ agonist. Although the compound has effects on several other receptors, many of the leading researchers/clinicians in schizophrenia biology have taken to calling aripiprazole the first “dopamine stabilizer” because of its D₂ partial agonist properties (Lieberman, 2004; Stahl, 2001; Tamminga, 2002). It should be noted that aripiprazole does not fit the characteristics of a selective presynaptic D₂-like agonist as was originally proposed (*vide supra*).

The idea of a partial agonist is intriguing because all partial agonists are also partial antagonists. The positive symptoms of schizophrenia are mediated by excess dopaminergic transmission in mesolimbic areas, and the partial agonist properties of aripiprazole compete with dopamine and cause partial antagonism, which provides clinical benefit. Conversely, in situations where extracellular dopamine concentrations are low (e.g., in dopamine circuits involved in working memory), partial agonists (e.g., aripiprazole) can occupy additional receptors and cause partial activation. Although aripiprazole looks like a low-to-moderate intrinsic activity partial agonist in many model systems (Burris et al., 2002; Lawler et al., 1999; Shapiro et al., 2003), other available data suggest that aripiprazole is a functionally selective D₂ ligand rather than a simple partial agonist. For example, the intrinsic activity and potency of aripiprazole for the D₂-mediated inhibition of cAMP accumulation is dependent on the cell line being studied: the drug demonstrates weak partial agonist activity in the CHO-D_{2L} cell line but strong partial agonist activity in HEK-D_{2L} cells (Burris et al., 2002; Lawler et al., 1999; Shapiro et al., 2003). Moreover, aripiprazole has been shown to have markedly different potencies at two D_{2L}-mediated functions within the same cell line (Urban et al., 2007b). Furthermore, aripiprazole completely antagonizes both D₂ agonist-mediated GTP γ S binding and GIRK channel activity in some cell systems (Shapiro et al., 2003), whereas it is a full agonist *in situ* for D₂-mediated inhibition of tyrosine hydroxylase (Kikuchi et al., 1995).

The wide array of D₂-mediated intrinsic activities and/or potencies observed for aripiprazole in different systems cannot be explained by classic pharmacology and suggests that aripiprazole is functionally selective (Urban et al., 2007a). These *in vitro* findings can also be correlated with the actions of aripiprazole *in vivo*, which are irreconcilable with the partial agonist hypothesis. One of the clearest examples is the effect of aripiprazole in the

unilaterally lesioned 6-hydroxydopamine (6-OHDA)-treated rat. Both full and partial dopamine agonists cause the 6-OHDA-lesioned rats to turn with high frequency in a tight contralateral fashion. 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 should also cause contralateral rotation; however, this effect was not observed (Kikuchi et al., 1995). Another less direct example 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). Similar to the reasoning espoused for schizophrenia, aripiprazole (as a partial agonist) should be very useful in treating these psychotic symptoms when added to the dopaminergic regimen of a PD patient; however, aripiprazole not only lacks effectiveness in treating the psychoses, it tends to worsen motor function (Friedman et al., 2006).

Although aripiprazole is a functionally selective D₂ ligand, aripiprazole also has actions at other receptors. Indeed, aripiprazole has high affinity for several receptors, including 5-HT_{1A}, and modest affinity for several others (Shapiro et al., 2003). Nonetheless, the interest in this compound revolves around its D₂ action. Because its intrinsic activity varies markedly depending on the signaling environment of the D₂ receptor (Lawler et al., 1999; Shapiro et al., 2003; Urban et al., 2007a), we believe the logical explanation to integrate the *in vitro* and *in vivo* data is functional selectivity at the D₂ receptor. If this hypothesis is true, a corollary is that compounds with similar D₂ partial agonist effects at adenylate cyclase might have very different clinical effects in treating psychoses. This latter hypothesis may be testable as other "partial agonists" (e.g., bifeprunox) are brought into clinical trials.

3. D₁-like signaling

D₁-like receptors couple to G $\alpha_{s/olf}$ and stimulate adenylate cyclase activity, which subsequently activates PKA and other signaling molecules. Although G α_s appears to mediate D₁-like receptor signaling, G α_{olf} also stimulates adenylate cyclase activity and is highly expressed in dopaminergic regions, such as the neostriatum, where there is little G α_s expression (Zhuang et al., 2000). Studies have also suggested that D₁ receptors couple to other heterotrimeric G proteins, such as G α_o and G α_q (Jin et al., 2001; Kimura et al., 1995; Wang et al., 1995). In addition, D₁-like receptors can mediate signaling at a variety of voltage-gated ion channels as well as NMDA and GABA_A receptors, either directly or indirectly, through actions on DARPP-32, the MAPK pathway, and other kinases and phosphatases. Moreover, there is evidence that dopamine receptors (and G proteins) can have other protein-protein interactions, such as receptor oligomerization or interactions with scaffolding or other regulatory proteins, which can also affect dopamine receptor signaling (Neve et al., 2004). D₁ receptor signaling can also occur through the $\beta\gamma$ subunits that form heterotrimers with G α_s or G α_{olf} , but less is known about these signaling mechanisms. For example, $\beta\gamma$ subunits can play a selective role in D₁-like signaling as D₁-mediated, but not D₅-mediated, adenylate cyclase activity is attenuated by depletion of the γ_7 subunit (Wang et al., 2001). Finally, as is typical for GPCRs, ligands can induce dopamine receptor internalization (Ryman-Rasmussen et al., 2007; Ryman-Rasmussen et al., 2005), and a recent study demonstrated a new role of endocytosis and endocytic machinery in dopamine

D₁ receptor signaling (Kotowski et al., 2011). It is too soon to know if this will impact the use of D₁ agonists in treatment of negative and cognitive aspects of schizophrenia.

The signaling cascades that are activated by D₁ receptors can also have long-term effects on cellular function by regulating transcription. Indeed, D₁ agonists increase cAMP, and cAMP phosphorylates cAMP response element binding protein (CREB) at Ser133, which regulates the transcription of many genes that are important to a variety of drug responses (Andrisani, 1999; Hyman et al., 1995; Minowa et al., 1996; Sands and Palmer, 2008). In addition, D₁ receptor activation can affect proteins in the MAPK signaling pathway, such as ERK (Brami-Cherrier et al., 2002). Interestingly, transcriptional changes in MAPK signaling molecules may be able to improve the therapeutic profile of D₁ agonists. Developing a functionally selective drug that selectively activates signaling molecules and pathways associated with the desired effects can improve a drug's therapeutic profile. For example, D₁ agonists may have the potential to improve prefrontal cortical functions and working memory in schizophrenic patients. Indeed, SKF81297 has been shown to improve recognition and memory by increasing the phosphorylation of CREB and DARPP32 in rat prefrontal cortex (Bateup et al., 2008; Hotte et al., 2006). Thus, developing functionally selective drugs that differentially activate aspects of CREB and DARPP32 signaling could have marked therapeutic utility.

Certain effects of novel drugs and potential D₁ ligands that have already been studied may not have been discovered because researchers may not have been examining the right pathway or using the right *in vitro* system to be able to observe effects. The concept of functional selectivity opens up exciting new opportunities for the development of many drugs, including APDs. Two decades ago, we found that D₁ binding sites in the amygdala were not associated with an appreciable stimulation of adenylate cyclase, which led us to hypothesize a novel species of D₁ receptor (Kilts et al., 1988; Mailman et al., 1986a; Mailman et al., 1986b). Molecular data over the next decade clearly demonstrated that these binding sites were actually the same D₁ receptor that is found in striatum, and the receptor activity was determined to represent a non-traditional mechanism(s) of signaling (Leonard et al., 2003a; Leonard et al., 2003b). Today, functional selectivity promises to provide more exciting findings in the drug discovery and development realm, and schizophrenia is one area where a functionally selective D₁ ligand could have a tremendous impact.

3.1. Evidence for Functional Selectivity at D₁-Like Receptors

3.1.1. Possible Mechanisms of D₁-Receptor Signaling that Could Evoke Functional Selectivity—Despite promising therapeutic potential for D₁ receptor agonists, few efforts have been made to investigate functional selectivity at D₁-like receptors. In regards to schizophrenia, D₁ agonists may have therapeutic potential for negative symptoms and cognitive deficits. In addition, D₁ agonists may even reduce the side effects associated with current APDs. A clearer understanding of D₁-like signaling pathways is critical for the identification and design of functionally selective D₁ compounds. This is complicated, however, because the signaling pathways activated by dopamine D₁ receptors are dependent on several factors: the cellular machinery in a given cell or experimental system (e.g., G proteins, β -arrestins, and GRKs), differences in membrane dynamics (e.g., highly lipophilic

neuronal cells vs. renal proximal tubular cells), and/or attenuation/potential of input signaling pathways (Mailman, 2007; Mailman and Huang, 2007; Neve et al., 2004). The most studied D₁ signaling cascade is the cAMP/PKA pathway. One signaling molecule in this pathway, DARPP32, can both inhibit and promote D₁ signaling, which provides an important mechanism for regulating dopaminergic signaling. Indeed, D₁-like receptor activation of PKA leads to a phosphorylation/dephosphorylation cycle of DARPP32 at Thr34 and Thr35, which results in inhibition of protein phosphatase 1 (PP1) (Greengard et al., 1999), whereas phosphorylation at Thr75 by Cdk5 results in DARPP32 inhibition of PKA. D₁-activated PKA can lead to the phosphorylation of other receptors in the cell (e.g., L-Ca²⁺ channels and NMDA) and inhibition of PP1, which prevents the dephosphorylation of many substrates, including the same receptors that are phosphorylated by PKA (Snyder et al., 1998). Although other pathways have been shown to be activated by D₁ receptors, many pathways are dependent on cAMP/PKA signaling.

The MAP kinase pathway, which plays important roles in growth and cell cycle control, may be a G protein-independent D₁ signaling pathway. Although few studies have investigated its role in D₁-like receptor signaling, arrestins have been shown to act as adaptor proteins for MAP kinase. For example, p-ERK has been found to form stable heterotrimeric complexes with the D₁ receptor and β -arrestin 2 (Chen et al., 2004). In addition, Nagai et al. (2007) revealed dose-dependent D₁ activation of ERK1/2 in the mouse prefrontal cortex that was blocked by a D₁ antagonist (but not a D₂ antagonist). Furthermore, β -arrestin 2 has been suggested to play a role in D₁-mediated ERK signaling (Urs et al., 2011). The mechanism(s) responsible for D₁-MAP kinase activation is unclear, but evidence suggests a dependence on the β -arrestin scaffolding protein. In addition, D₁ effects on MAP kinases may link D₁ signaling with other neurotransmitters, such as glutamate. Studies have clearly shown that D₁ receptors activate ERK in striatal MSNs, but further studies must be carried out to gain a clearer understanding of the mechanisms that are involved.

D₁ dopamine receptors are also involved in calcium signaling. Calcium is a dynamic but tightly regulated second messenger pathway that is differentially controlled across non-nervous and nervous tissue. The slow IP₃-mediated pathway via phospholipase C predominates in non-excitable cells. In excitable cells, however, voltage-dependent Ca²⁺ channels (L, N, and P/Q type) play a greater role and balance Ca²⁺ intake/output from the cell. D₁-like receptors are positively coupled to L-type channels and negatively coupled to N and P/Q-type Ca²⁺ channels (Surmeier et al., 1995). Interestingly, studies have shown that D₁ receptors can directly interact with N-type calcium channels, and D₁ activation has been shown to inhibit N-type calcium channels (Kisilevsky et al., 2008). We previously mentioned that many D₁-mediated pathways are dependent on cAMP/PKA signaling, and this also appears to be the case for D₁-mediated inhibition of voltage-gated calcium channels (Fienberg et al., 1998). For example, D₁-stimulated L-type Ca²⁺ channels have been shown to lead to PKA-dependent potentiation and PKC-dependent suppression of currents in rat prefrontal cortical neurons (Young and Yang, 2004).

3.1.2. Phospholipase C as a D₁ Signaling Mechanism—Phospholipase C (PLC) hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP₂) to produce 1,2-diacylglycerol

(DAG) and inositol 1,4,5-trisphosphate (IP₃). The latter binds to the IP receptor and stimulates the release of Ca²⁺ from intracellular stores within the endoplasmic reticulum. Diacylglycerol recruits protein kinase C (PKC) to the membrane, which leads to a variety of effects, including NF-κB activation and actin reorganization. Phospholipase C may be activated by both Gα_q and Gβγ, and all four members of the Gα_{q/11} family (α_q, α₁₁, α₁₄, α₁₆) have been shown to activate PLC-β isoforms (Hepler et al., 1993; Kozasa et al., 1993; Lee et al., 1992). In addition, Gβγ subunits can activate PLC-β, and the composition of specific Gβγ subunits affects the potency for PLC-β (Boyer et al., 1994). Both Gα_q and Gβγ play a role in PLC-β activation (either on their own or synergistically), and the finding that PLC-β has distinct sites for Gα_q and Gβγ activation (Runnels and Scarlata, 1999) has important consequences for functional selectivity. Moreover, if both cAMP/PKA and PLC signaling occur via D₁ receptors, then drug discovery efforts could potentially exploit specific signaling properties of ligands.

To truly test the functional selectivity of compounds, researchers must identify independent signaling pathways because signaling pathways that are dependent on other pathways can confound the results. In addition, various *in vitro* systems are needed to properly test functional selectivity because the signaling machinery may be different in different cell lines (i.e., not all cell lines are appropriate for testing certain signaling pathways). For example, one study showed that D₁-linked PLC was dependent on PKA activation in LTK⁻ cells (Yu et al., 1996); however, the predominant PLC isoform that was believed to be involved (i.e., PLC-β₂) is not expressed in LTK⁻ cells. The study concluded that PLC-γ was responsible for the observed activity, but different results may have been obtained if the model system contained PLC-β₂. Although a recent study of D₁ effects on intracellular Ca²⁺ currents supported the idea of Gα_q-mediated PLC activation, this mechanism was found to be co-dependent on a cAMP/PKA signal (Dai et al., 2008). In addition, measurements of intracellular Ca²⁺ currents may be influenced by additional sources other than PLC stimulation. Indeed, similar data have been observed in other studies, and there is a strong possibility that changes in Ca²⁺ can result from a D₁-mediated non-PLC Ca²⁺ mechanism (Lin et al., 1995).

3.1.3. Implications and Complications of Purported D₁-mediated PLC

Signaling—Non-cyclase D₁-mediated signaling clearly occurs (Leonard et al., 2003a; Leonard et al., 2003b; Mailman et al., 1986a), and evidence for a cAMP/PKA-independent signaling pathway has been shown in studies of adenylate cyclase V deficient mice (Iwamoto et al., 2003). Although 85-90% of cyclase activity was abrogated in these mice, D₁-mediated locomotion was enhanced. Such findings are direct evidence for the possibility of discovering D₁ functionally selective compounds. Unlike the D₁ actions on cAMP/PKA, the importance of PLC in direct D₁ signaling is controversial. Indeed, several studies have suggested concurrent Gα_{q/11} and Gα_{s/olf} coupling to the D₁ receptor (Mannoury la et al., 2007; Panchalingam and Undie, 2000; Wang et al., 1995), and a recent report indicated differential coupling by SKF83959 (Rashid et al., 2007b).

Our group originally (and mistakenly) hypothesized that these non-adenylate cyclase-linked effects might represent a D₁-like receptor from a different superfamily that had similar pharmacology to the known D₁-like receptors (Mailman et al., 1986a). We quickly

determined that the non-adenylate cyclase effects were more likely to be generated by the same gene product utilizing different signaling machinery (Kilts et al., 1988; Leonard et al., 2003a; Leonard et al., 2003b). Interestingly, another group subsequently resurrected the hypothesis of a novel “D₁-like” receptor (Friedman et al., 1997; Undie et al., 1994), and those data are very relevant to the issue of D₁ functional selectivity.

The data in support of the hypothesis for a novel D₁-like receptor came from D₁ ligand activation of PLC; however, limitations in the designs of the studies that have supported this hypothesis have raised doubts about whether the signaling is really D₁ mediated. For reasons that are unclear, the concentrations of the drugs used in the published experiments have always been suprapharmacological (10 μ M or greater, orders of magnitude higher than the affinities of the compounds). Moreover, there are good correlations between the binding affinities of D₁ ligands and their potencies at activating adenylate cyclase, but these correlations were not observed between binding and PLC activation. Although functional selectivity can be expressed as large changes in potency and/or intrinsic activity (Gay et al., 2004; Mailman, 2007; Mailman and Gay, 2004; Urban et al., 2007a; Urban et al., 2007b), the combination of a requirement for high drug concentrations and SAR discordance in studies demonstrating D₁-mediated PLC signaling may be a red flag.

To further investigate whether D₁ receptors can couple to G α_q and signal through PLC, similar studies to the previously published reports that showed D₁-mediated PLC signaling were repeated in D₁ knockout mice. Importantly, the D₁-mediated adenylate cyclase activity was abolished in the D₁ knockout mice (Friedman et al., 1997), but PLC activation was similar to the wild-type controls. The conclusion from this study was that this was evidence for a novel D₁ receptor (Friedman et al., 1997); however, an equally plausible explanation is that the PLC signaling was not D₁ mediated. In support of the latter explanation, none of the known or orphan GPCRs have been matched to this proposed new D₁-like receptor. Moreover, in D₁ knockout mice, there is a profound decrease in phenylbenzazepine binding sites (Montague et al., 2001), which makes it highly unlikely that the pharmacological properties of benzazepines would be unaffected if this was a D₁ effect. Furthermore, the purported D₁-like G α_q -coupled receptor does not react with a D₁ receptor antibody (Jin et al., 2001). Taken together, the evidence may favor the hypothesis that these PLC effects are mediated by a non-dopamine receptor binding site that can be activated with low potency by one class of dopamine ligands (i.e., phenylbenzazepines) (Leonard et al., 2003a). Interestingly, a more recent study demonstrated that the PLC activity induced by benzazepines was abolished in D₅ knockout mice (Sahu et al., 2009).

In addition, several recent studies have suggested that phenylbenzazepine-based D₁ ligands may actually signal through the PLC pathway in a functionally selective fashion. For example, a functional D₁/D₂ dimer has been reported to be activated by one phenylbenzazepine (SKF83959) but not another (SKF83822). Interestingly, this correlates with the suggestion that SKF83959 selectively activates D₁-linked G α_q , whereas SKF83822 selectively affects G α_s (Lee et al., 2004; Rashid et al., 2007b), and these studies support the importance of PLC/G α_q signaling through D₁ receptor heterodimers (e.g., with D₂) (Rashid et al., 2007a). The signaling of D₁/D₂ heterodimers have recently been reviewed (Hasbi et al., 2011), but the physiological relevance of D₁/D₂ heterodimer signaling is controversial

because studies have shown that most striatal neurons do not co-express D₁ and D₂ receptors (Valjent et al., 2009). Further studies are needed to clarify whether D₁ receptors can directly activate G α_q and signal through the PLC pathway. If the PLC pathway is important for D₁ signaling, then certain phenylbenzazepines (and possibly D₁ ligands of other chemical classes) may be highly functionally selective (Ryman-Rasmussen et al., 2007; Ryman-Rasmussen et al., 2005), and the PLC signaling pathway may provide a route to the development of novel drugs.

3.1.4. Direct Evidence for Functional Selectivity at the D₁-Like Receptors—

Functional selectivity has been difficult to demonstrate for D₁-like dopamine receptors because of the lack of clear effectors coupled to the receptor. Nevertheless, one study investigated the adenylate cyclase activation and receptor internalization induced by a variety of structurally different D₁ agonists with various affinities for D₁ receptors (Ryman-Rasmussen et al., 2005). Interestingly, the Ryman-Rasmussen et al. study identified several D₁ agonists that activate adenylate cyclase with great efficacy but fail to cause receptor internalization. Importantly, internalization efficacy was found to be independent of agonist structural class and agonist affinity, suggesting that functional selectivity at D₁ receptors cannot be predicted by simple structural examination of D₁ agonists.

A subsequent study by Ryman-Rasmussen et al. (2007) compared the ability of dopamine and two structurally dissimilar agonists, A77636 (chemically an isochroman) and dinapsoline (DNS; chemically an isoquinoline), to regulate receptor internalization and trafficking. Both A77636 and DNS are full agonists at activating adenylate cyclase, and DNS exhibited a similar efficacy to dopamine in causing internalization, whereas A77636 caused significantly greater internalization. An investigation of the post-endocytic agonist effects on receptor trafficking revealed significant differences in agonist regulation of receptor trafficking. Dopamine caused the D₁ receptor to recycle back to the cell surface within 1 h, whereas the D₁ receptor persisted intracellularly for up to 48 h after the removal of A77636. Surprisingly, DNS caused the receptor to recycle back to the membrane after 48 h. Pulse-chase experiments and the use of actinomycin D to inhibit new protein biosynthesis demonstrated that cell surface recovery was not due to the synthesis of new proteins. Taken together, these data indicate that agonists target D₁ receptors to different intracellular trafficking pathways.

3.1.5. Potential Utility of D₁ Functionally Selective Drugs—The D₁-like receptors have been implicated as therapeutic targets for numerous CNS disorders, such as Parkinson's disease (Mailman et al., 2001; Taylor et al., 1991), schizophrenia, learning and memory dysfunctions (Arnsten et al., 1994; Goldman-Rakic et al., 2004), and attention deficit hyperactivity disorder (Heijtz et al., 2007). Importantly, D₁ agonists may play a critical role in the treatment of the negative and cognitive symptoms of schizophrenia, which are not very responsive to current drugs. One of the issues that has been associated with the development of a selective full D₁ agonist is side effects (e.g., hypotension and tachycardia) (Huang et al., 2001). Utilizing the concept of functional selectivity, however, we can potentially design a D₁ agonist that interacts with specific signaling pathways to enhance the beneficial effects while avoiding unwanted side effects. For example, sodium levels play a

critical role in regulating blood pressure, and the hypotension and tachycardia that are observed with D₁ agonists result from excessive stimulation of peripheral D₁ receptors, which can influence sodium concentrations. Although the D₁-linked signaling cascade(s) regulating sodium transport are not entirely clear, evidence suggests that D₁ receptors primarily modulate sodium resorption via the Na⁺/H⁺-exchanger and Na⁺-K⁺-ATPase (Hussain and Lokhandwala, 1998). Thus, the design of a D₁ agonist that is less efficacious at these or other currently unidentified transduction pathway(s) could permit the use of high doses of a D₁ agonist in patients.

Although functional selectivity has a lot of promise for the discovery and development of D₁ ligands, a lot more knowledge is required to take full advantage of functional selectivity. For example, instead of just determining the binding characteristics and whether a drug is an agonist or antagonist at D₁ receptors, researchers must understand which signaling pathways are activated by a given drug and which signaling pathways are critical for the desired effects of the drug. A thorough understanding of these issues will allow scientists to manipulate the chemical structures of novel D₁ ligands to selectively activate signaling pathways. Interestingly, studies have shown that major ligand structural differences cannot explain differences in functional selectivity at the D₁ receptor; thus, functional selectivity could be due to more subtle structural changes or to the G proteins and other signaling molecules that are coupled to D₁ receptors in various brain regions. With the acceptance of functional selectivity and the ability to selectively modulate cellular functions in a much more specific manner than previously imagined, researchers have questioned whether diseases could be treated by modulating signaling pathways rather than directly targeting receptors. This strategy has flaws, however, because many of the signaling pathways that are mediated by dopamine receptors have critical functions throughout the body; thus, just targeting the signaling pathway would likely result in many serious side effects. Indeed, functionally selective ligands that target dopamine receptors could be designed to affect a specific signaling pathway, but the effects could be localized to dopaminergic diseases by activating or inhibiting a specific pathway through dopamine receptors.

Superficially, a D₁ agonist seems counterintuitive for the treatment of schizophrenia; however, the differential localization and functional characteristics belie this. In addition, functionally selective D₁ agonists might further improve the therapeutic index of drugs used to treat cognitive and/or negative domains of schizophrenia and related disorders. Interestingly, the primary function of almost all clinically used dopamine antagonists is the treatment of schizophrenia and other psychotic or manic disorders. All clinically used dopamine agonists (approved for a variety of disorders other than schizophrenia) were designed as D₂ agonists (i.e., no clinically used dopaminergic drugs were designed as D₁ agonists). Because so much of the focus of dopaminergic diseases, especially schizophrenia, has been aimed at D₂ receptors, full D₁ agonists have gone largely unnoticed. Whereas several studies have demonstrated that D₁ antagonists would not be effective APDs (Den Boer et al., 1995; Karlsson et al., 1995), there is a large body of experimental research showing that D₁ agonists can improve working memory processes in the prefrontal cortex (Arnsten et al., 1994; Cai and Arnsten, 1997; Castner et al., 2000; Goldman-Rakic et al., 2004; Hersi et al., 1995; Lidow et al., 1991; Schneider et al., 1994; Steele et al., 1997) as well as other functions (Han et al., 1997; Shohamy and Adcock, 2010). Importantly, the

large body of data supporting the potential beneficial effects of D₁ stimulation in cognition and memory also shows a clear dose-dependency for these effects. Indeed, higher doses of a D₁ agonist have been demonstrated to impair memory performance in aged monkeys (Castner et al., 2000). The involved mechanisms by which D₁ receptors affect memory and cognition are not fully understood, but a functionally selective D₁ ligand might be able to avoid the biphasic dose-response relationships and only activate the signaling pathway(s) that enhance cognition. Such examples illustrate how the elucidation of mechanisms of functional selectivity of dopamine receptor ligands may have clinical relevance as well as intrinsic heuristic value.

Although numerous D₂-like ligands have been the subject of clinical studies, the only reports of studies in humans for selective D₁ agonists are for DHX (Brewster et al., 1990; Lovenberg et al., 1989; Mottola et al., 1992) and ABT-431 (nee A83959) (Michaelides et al., 1995; Shiosaki et al., 1996). Both compounds have similar pharmacology and have been shown to have profound antiparkinson activity (Giardina and Williams, 2001; Haney et al., 1999; Okumu et al., 2002; Rascol et al., 1999; Rascol et al., 2001; Self et al., 2000). Both compounds have little oral bioavailability, and only DHX remains available for clinical testing (George et al., 2007; Mu et al., 2007) with a phase IIa study as a cognitive enhancer in schizophrenia currently ongoing (Slifstein et al., 2011). If positive results come from such studies, it will spur efforts to discover compounds with better pharmacokinetics and, possibly, functionally selective signaling properties.

4. Conclusion

Current APDs are relatively effective at treating the positive symptoms of schizophrenia, but unwanted side effects and a lack of efficacy in treating negative and cognitive symptoms have highlighted the need for new and improved APDs. Although newer generation antipsychotics may have important therapeutic effects at receptors other than the dopamine receptor, all currently approved APDs share actions at D₂ receptors. With the growing acceptance of functional selectivity and in-depth mechanistic studies into the signaling pathways mediated by dopamine receptors, this is an exciting time for the discovery of APDs. Current high-throughput screening assays for novel APDs that only examine effects on the cAMP pathway may be missing potential therapeutic compounds. Drug discovery efforts should also examine other signaling pathways that are activated by D₁ and D₂ receptors and search for functionally selective compounds. The primary target for APDs is the dopamine receptor system, but a thorough understanding of the dopamine-mediated signaling pathways that are responsible for the specific effects of schizophrenia will help to focus drug discovery and development efforts. Although current APDs are effective at treating the positive symptoms of schizophrenia, they are not very effective at treating negative symptoms and cognitive deficits. In addition, current APDs have significant side effects. The improvements that have been made from typical antipsychotics to atypical antipsychotics and newer functionally selective drugs, such as aripiprazole, highlight the possibility of improving APDs, and the design of novel functionally selective drugs holds promise for the treatment of schizophrenia.

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Figure 1.

The implications of functional selectivity at the dopamine D₂ receptor are illustrated in this cartoon. Functionally selective drugs, unlike dopamine, might differentially affect both canonical and non-canonical signaling pathways. This could result in differential acute effects, which is illustrated by the center and right hand aspects of the figure. For example, a ligand would cause differential effects on mediators of acute action (e.g., the dopamine-induced hyperpolarization of a cell mediated via inward-rectifying potassium channels and acute actions of cAMP) as well as the longer term effects of drugs. Thus, changes in transcription initiated by cAMP on mechanisms like CREB could be altered by some drugs in a different manner than receptor-initiated changes in transcription initiated by β -arrestin2/Akt.