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# Novel Dopamine Therapeutics for Cognitive Deficits in Schizophrenia

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## Abstract

Schizophrenia is characterized by profound cognitive deficits that are not alleviated by currently available medications. Many of these cognitive deficits involve dysfunction of the newly evolved, dorsolateral prefrontal cortex (dlPFC). The brains of patients with schizophrenia show evidence of dlPFC pyramidal cell dendritic atrophy, likely reductions in cortical dopamine (DA), and possible changes in DA $D_1$ receptors ($D_1R$). It has been appreciated for decades that optimal levels of DA are essential for dlPFC working memory function, with many beneficial actions arising from $D_1R$ stimulation. $D_1R$ are concentrated on dendritic spines in the primate dlPFC, where their stimulation produces an inverted U dose-response on dlPFC neuronal firing and cognitive performance during working memory tasks. Research in both academia and the pharmaceutical industry has led to the development of selective $D_1$ agonists, e.g., the first full $D_1$ agonist, dihydrexidine, which at low doses improved working memory in monkeys. Dihydrexidine has begun to be tested in patients with schizophrenia or schizotypal disorder. Initial results are encouraging, but studies are limited by the pharmacokinetics of the drug. These data have, however, spurred efforts towards the discovery and development of improved or novel new compounds, including $D_1$ agonists with better pharmacokinetics, functionally selective $D_1$ ligands, and $D_1R$ positive allosteric modulators. One or several of these approaches should allow

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optimization of the beneficial effects of $D_1$R stimulation in the dlPFC that can be translated into clinical practice.

**Keywords**

prefrontal cortex; D1 agonist; working memory; schizophrenia; executive function; D2 receptors

## General Introduction

Drugs targeting dopamine (DA) receptors have been a cornerstone of schizophrenia pharmacotherapy for more than a half-century. To date, all approved antipsychotic drugs target DA $D_2$ receptors ($D_2$R), and although these agents can reduce positive symptoms, improvement of cognitive function, if any, is modest and difficult to dissociate from other drug effects (1, 2). Schizophrenia involves profound dysfunction of the newly evolved, dorsolateral prefrontal cortex (dlPFC). The pioneering research of Patricia Goldman-Rakic uncovered the neuronal circuits in dlPFC that generate the mental representations needed for working memory that are the foundation of abstract thought. She discovered that the dlPFC is greatly influenced by DA, as DA depletion causes profound impairment in working memory (3). Thus, enhancing DA's beneficial actions is a logical approach to ameliorating cognitive deficits.

Five DA receptor genes encode six receptors in humans ($D_1$, $D_{2L}$, $D_{2S}$, $D_3$, $D_4$, $D_5$). Two of these, the $D_1$ and $D_5$, are very homologous such that no current drugs are adequately selective for them. Because of this, when we refer to $D_1$ agonists or antagonists we mean compounds that bind to both $D_1$ and $D_5$ receptors. The members of the $D_2$-like family include the $D_{2L}$ and $D_{2S}$ (splice variants), $D_3$, and $D_4$ receptors. Although there are some selective ligands for these subtypes, except where noted, our references to $D_2$ drugs will indicate compounds with modest or no selectivity among $D_{2L}$, $D_{2S}$, $D_3$ or $D_4$ receptors. We shall focus on the rationale for DA therapeutics as cognitive-enhancers, specifically the role of the $D_1$ receptor ($D_1$R).

## Dopamine influences on the dlPFC microcircuits afflicted in schizophrenia

Schizophrenia is characterized by striking deficits in cognitive function, especially the higher cognitive operations that depend on the dlPFC. In contrast to rodents, DA axons project throughout most of the primate cortex, with greatest innervation of the motor cortices and least in the primary visual cortex. The DA neurons that project to the dlPFC are likely "salience" cells that fire in response to both rewarding and aversive events, e.g. during stress exposure. Analyses of post-mortem brain tissue have identified grave insults to the layer III microcircuits that subserve working memory, including spine loss and underactivity of layer III pyramidal cells (4). In monkeys, these pyramidal cells generate the persistent firing needed for working memory, whereas GABAergic interneurons refine the tuning of the circuits. Together, they generate the mental representations, the foundation of abstract thought, that keep information "in mind" in the absence of sensory stimulation. These neurons are termed "Delay cells," and their activity is greatly influenced by $D_1$R, but not $D_2$R stimulation.

Thus, studies of the actions of DA receptors in the primate dlPFC (reviewed in 5) have shown that optimal levels of $D_1$R stimulation are essential for working memory function. Layer III pyramidal cells excite each other through NMDA receptor (NMDAR) synapses on spines; NMDAR channel opening depends on cholinergic stimulation of nicotinic $\alpha_7$ receptors ($\alpha_7$nChR) within the glutamate synapse (6). Defects in both NMDAR and $\alpha_7$nChR have been linked to schizophrenia. $D_1$Rs are concentrated on layer III spines, and can even be found within the synapse (Figure 1A). $D_1$Rs are often co-localized with HCN (Hyperpolarization-activated cyclic nucleotide gated) channels on spines; $D_1$R mediated increases in cAMP open HCN channels and reduce synaptic efficacy (Figure 1A). The effects of $D_1$R stimulation on Delay cell firing are schematically summarized in Figure 1B. Evidence suggests that low levels of $D_1$R stimulation increase firing by maintaining NMDAR within the synapse, whereas slightly greater $D_1$R activity sculpts away "noise" by gating out non-preferred inputs via HCN channel opening (7). Conversely, high levels of stimulation (e.g., as occur during stress) suppress all firing. This results in an inverted U dose response to $D_1$ agonists seen at the behavioral level. As described below, there is evidence of reduced DA levels in the dlPFC in schizophrenia, and thus therapeutic strategies have focused on enhancing $D_1$R stimulation. Of particular relevance to treatment development for schizophrenia, Castner et al. (8) found that intermittent, trace doses (0.00001–0.0001 mg/kg) of a $D_1$ agonist could ameliorate working memory deficits induced in monkeys by haloperidol, effects possibly due to indirect down-regulation of $D_1$ receptors caused by haloperidol. These data spurred efforts to determine if low levels of $D_1$R stimulation could improve cognitive function in patients.

## Approaches to modulating dopamine function

### $D_1$ antagonists

As the understanding of $D_1$R microcircuitry was evolving, and the first selective antagonist SCH23390 (Figure 2) was reported (9), one prevalent hypothesis was that $D_1$R antagonists might be novel treatments for schizophrenia (10). SCH-23390 has pharmacokinetic limitations, but its analog SCH39166 (ecopipam, Figure 2) had improved properties (11). Ecopipam was studied clinically for a variety of indications, including schizophrenia (12–15), drug abuse (16), and obesity (17), but in each case undesirable effects were observed. In addition to the basic neurobiology discussed above, it was "back-translation" of the observations with $D_1$R antagonists [e.g., induction of preclinical amotivational states and cognitive deficits (18)] that increased the interest in therapeutic utility of $D_1$ agonists. These antagonists have, however, continued to impact neuroscience because $^{11}$C-SCH-23390 and its closely related analog, $^{11}$C-NNC-112 (Figure 2), have become the mainstay PET ligands for clinical imaging of $D_1$Rs (19, 20), including studies which demonstrate direct relationships between $D_1$R binding potential and cognitive function (21, 22) (see below).

### Indirect activation of dopamine receptors

A variety of strategies have been employed to try to enhance DA actions in the dlPFC. Mechanisms such as DA transporter (DAT) inhibition, increased DA synthesis or release, or inhibition of degradation by monoamine oxidases (MAO) or catechol-O-methyl-transferase (COMT) can augment the amount of synaptic catecholamines, including DA. Yet

therapeutically, generalized increases in catecholamine actions (e.g., levodopa, methylphenidate, amphetamines) will tend to cause undesired side effects, especially in many target populations who are susceptible to exacerbation of psychoses, to substance abuse, etc., that can be affected by activation of $D_2R$. As DAT expression is low in the dlPFC, it has been hypothesized that COMT might be an excellent target for more selective regional activation, albeit of all catecholamine receptors (23, 24). Unfortunately, the three approved COMT inhibitors (tolcapone, entacapone, ocicapone) (25, 26), while useful for slowing the peripheral degradation of levodopa in treatment of Parkinson's disease, have little brain penetration (27, 28). Rigorous testing of this hypothesis must await a non-toxic brain penetrant COMT inhibitor. This suggested that targeting specific dopamine receptors, especially the $D_1R$, might be a useful strategy.

## Concepts relevant to dopamine receptor ligands

Clinical and basic neuroscientists are generally aware of the classical issues in the use of receptor-targeting drugs, specifically the affinity of the drug for the desired versus off-target receptors, and the property of the drug (e.g., agonist or antagonist) at the primary targeted receptor. There are two directly important subtleties that can often impact interpretation, but are less widely appreciated. The classical one is partial agonism, reflecting that a particular drug even at near-saturating concentrations will only activate the target receptor to some fraction of the natural ligand of the receptor. (The degree to which a drug activates a receptor relative to the natural ligand for the receptor is called *intrinsic activity*.) Classically, partial agonists are also known to be partial antagonists, and may inhibit the actions of the natural ligand. The second and now generally accepted concept is called "functional selectivity" or "ligand bias" (29–31). Essentially, this concept reflects the fact that some drugs can have very diverse functional effects on different signaling pathways mediated by a single receptor. In the extreme, this can even be full activation (full agonism) of one signaling pathway of a receptor, and pure antagonism at another pathway of the same receptor even in the same cell (32, 33). This differential activation may also be expressed as large differences in potency at two different signaling pathways (29, 34).

Finally, the concept of allosteric drugs (i.e., ligands acting at sites on the receptor distant from the binding site of endogenous ligands) is well known in biological psychiatry as the mechanism of action at ionotropic receptors (e.g., benzodiazepines at $GABA_A$ receptors). Recently, there has been a surge of activity in the discovery of allosteric ligands for G protein-coupled receptors, and this is beginning to impact DA receptors. These three concepts will be relevant to specific compounds discussed below.

## Non-selective drugs with $D_1$ agonist properties

There is sometimes confusion when there is discussion of approved "DA agonists," and a brief discussion may be useful All of the currently approved "dopamine agonists" are selective to a greater or lesser extent for the $D_2$-like versus the $D_1$-like receptors. Indeed, many (e.g., ropinirole, pramipexole, bromocriptine, cabergoline) are devoid of $D_1$ agonist activity, though there are three exceptions. Apomorphine has $D_1R$ high intrinsic activity, but is selective for $D_2R$; its activity at $D_1R$ may be why it is effective in advanced Parkinson's Disease (PD) (35). Unfortunately, its poor pharmaceutical properties and $D_2R$ side effects

make it unsuitable for treating cognition (36–41). Rotigotine has similar properties. Pergolide, which will soon be unavailable, has modest $D_1$ partial agonist activity (42, 43), and has been used for cognitive experiments as discussed below. Lastly, CY-208,243 had modest selectivity for $D_1$ versus $D_2$ receptors (44), and $D_1$-dependent antiparkinsonian actions in monkeys (45–47), (but not in humans (48)), but its development ceased. Ergolines are generally promiscuous for monoamine receptors, and many activate serotonin 5-$HT_{2B}$ receptors (49) making them unsuitable for human studies.

## Selective $D_1$ agonists used in laboratory animal studies

The prototype of selective $D_1$ agonists is SKF-38393 (Figure 3), first reported nearly forty years ago (50, 51), which is a member of the 1-phenyl-tetrahydro-benzazepine chemotype that has yielded dozens of experimental compounds (52–54). SKF-38393 probably has been the most widely used $D_1$ agonist, but although it is quite selective, it is only a partial agonist with modest intrinsic activity in canonical signaling pathways (51, 55–57). When this is ignored in interpreting pharmacological studies, it may lead to erroneous conclusions. SKF-81297 (Figure 3) is another commonly used member of the benzazepine chemotype that has much higher intrinsic activity than SKF-38393 (57), and has been a useful tool for *in vitro* and animal experimentation.

Two $D_1$ agonists from this class, SPD-451 and SKF-83959, have been particularly provocative because both were proposed to be functionally selective $D_1$R ligands that had high intrinsic activity for $D_1$R-activation of phospholipase C and low intrinsic activation for the canonical cAMP-mediated signaling. Extensive studies with SKF-83959 also led to the hypothesis that its novel functionally selective signaling was mediated by a $D_1D_2$ receptor heterodimer (58). The development of SPD-451, originally advanced by CeNeS Pharmaceuticals plc and later Shire, has apparently ceased. SKF-83959 has never been advanced to humans, but has been widely used experimentally because of these purported novel properties (59–62). Unfortunately, recent data suggest that this compound is actually similar to other benzazepine partial agonists, and is neither highly functionally selective, nor works through a $D_1/D_2$ heterodimer (63–65). As a class, the benzazepines also have poor oral bioavailability and short duration of action due to the inherent catechol group (66), and in addition, many of the members of this group have a propensity to cause seizures (67).

## Non-benzazepine centrally available full $D_1$ agonists

The first full $D_1$ agonists were fenoldopam and SKF-89626 (Figure 3), but neither compound was brain penetrable (57, 68, 69). The first selective centrally available $D_1$R full agonist was dihydrexidine (Figure 3) (55–57, 70–73), and it has been a very useful tool in testing hypotheses about the roles of $D_1$R receptors, such as for antiparkinsonian therapy (74) or effects on cognition (75). Although dihydrexidine is only ten-fold $D_1$:$D_2$ selective (72), it has profound $D_2$R functional selectivity (32, 33), and its behavioral effects generally lack $D_2$R properties (76). Dihydrexidine, however, has two major limitations for human experimentation: it has very little oral bioavailability, and is metabolized very rapidly.

Chronologically, the next compounds of importance were A-68930 and A-77636 (Figure 3), two selective $D_1$ agonists from the novel isochroman chemotype (77, 78). A-68930 caused

seizures (79), but A-77636 has been widely used experimentally because it appeared to have overcome the bioavailability problems of dihydrexidine and had a long duration of action. In murine and primate species, both compounds caused profound antiparkinsonian effects like dihydrexidine (80, 81), but both also caused a profound and rapid tolerance (78, 82–84). Both the tolerance and seizures are potential developmental liabilities that are discussed below.

Because of the tolerance caused by A-77636, Abbott laboratories next reported A-86929 (Figure 3) and its diacetyl prodrug ABT-431 (adrogolide) (Abbott Laboratories). A86929 is similar in structure and pharmacological properties to dihydrexidine (85, 86). Like dihydrexidine, ABT-431 caused dramatic antiparkinsonian effects (74, 86, 87), but like dihydrexidine, even the prodrug ABT-431 had poor oral bioavailability. ABT-431 was out-licensed to Drug Abuse Sciences as a potential anti-cocaine therapy, but development ceased for reasons that are not public. Another compound that failed development was dinapsoline, a $D_1$:$D_2$ agonist with high $D_1$R intrinsic activity and significant functional selectivity at $D_2$ receptors. Like dihydrexidine, its behavioral actions in animal models of Parkinson's models were $D_1$R, not $D_2$R, dependent (88–90). Unfortunately, there have not been newer compounds with marked advantages reported recently.

## Challenges and opportunities for clinical development

A major problem in development of selective full $D_1$ agonists has been oral bioavailability. All reported chemotypes for selective full $D_1$ agonists contain a catechol moiety (as in dopamine) that, at least to date, seems necessary for full $D_1$R agonism but which causes predictable problems in bioavailability. In the few cases where drugs have reasonable bioavailability (e.g., A-77636 (78) or dinapsoline (89)), the compounds had high plasma protein binding and low free fraction, and unbound clearance remains high. A-77636 also has near irreversible binding to the $D_1$R *in vivo* (91). Addressing these pharmacokinetic issues is essential for any major advance.

There are two primary safety concerns with this class. Some $D_1$ agonists have been reported to induce seizures or lower seizure thresholds, and $D_1$ activation seems to be critical as they are prevented by $D_1$R antagonists and not seen in $D_1$R knockout mice (67). This is drug specific, however, as the full $D_1$ agonist A-77636 does not induce seizures, unlike its analog A-68930 (79). Similarly, monotherapy with dihydrexidine or ABT-431 has not been associated with epileptogenic potential in rats, mice, or primates. Thus, $D_1$R activation alone is not sufficient to cause seizures, and the involved mechanism(s) and the relative safety margin of $D_1$ agonists as a class are unclear.

The other $D_1$R-related safety concern is hypotension, the reason for the premature termination of the first pilot human trial of dihydrexidine (92). These effects are probably mediated by peripheral $D_1$R in the kidney and elsewhere in the cardiovascular system (93). Because the cardiovascular system can respond rapidly to such challenges, this may not be limiting if blood concentrations of the drug do not rise too rapidly as suggested by recent clinical studies (58, 94, 95).

Finally, a non-safety issue, rapid tolerance, may limit use of $D_1$ agonists. During antiparkinsonian studies in both murine and primate species, the dramatic effectiveness of A77636 and A68930 was rapidly (within 24–48 h) lost (82, 96). Indeed, a single dose of A77636 results in almost complete tolerance (Blanchet et al., 1996), hypothesized to be due to rapid desensitization probably resulting from irreversible binding to the $D_1$R (91). On the other hand, the fact that dinapsoline (a drug that does not bind irreversibly) did not cause tolerance with once or twice daily subcutaneous injection, but did with constant minipump infusion (89), suggests more complicated mechanisms. When a clinical candidate is identified, it will be important to determine the conditions under which it may cause this rapid tolerance.

## Dopamine changes in schizophrenia

The initial hypotheses about the mechanism of positive symptoms of schizophrenia were based in large measure on pharmacological data in which the clinical effectiveness of antipsychotic drugs correlated well with their affinity for $D_2$-like receptors (97). Even today, all approved antipsychotics require as part of their pharmacology interactions with the $D_2$R. The antipsychotic drugs are generally effective against positive symptoms (e.g., delusions, hallucinations, etc.) (98, 99). A variety of clinical experimental studies showing that sensitivity to stimulant medications (100–103), increases in DA synthesis (104–106), and predictive utility of baseline occupancy of striatal $D_2$Rs (107) suggest that increased activity in striatal DA neurotransmission is associated with positive symptoms (108), explaining the efficacy of $D_2$R antagonists.

Conversely, effects on negative symptoms are limited (109–112). Effects on neurocognitive deficits (e.g., working memory, verbal memory, attention, executive functioning) have also been reported (1, 2, 113–118), but have been small (99). The relative lack of effects of antipsychotic medications on cognition are particularly important given that approximately 75% of patients with schizophrenia have clinically meaningful deficits in at least two cognitive domains, and 90% have deficits in at least one domain (119). In addition, cognitive deficits are present at illness onset (120), persist over time (121), and are more predictive of overall psychosocial functioning than are positive symptoms (122, 123).

Negative symptoms and cognitive deficits are thought to be related, at least in part, to a cortical DA deficit (124–126). An abundance of preclinical and other indirect data suggest that hypodopaminergic function in the dlPFC may be associated with these symptom domains. As described above, either DA depletion in the dlPFC, or DA antagonists, impair cognitive function (3, 127–129). $D_1$ agonists can reverse these deficits (75), although higher doses of $D_1$ agonists impair working memory function, leading to inverted-U dose-response curves (75, 130–133).

Evidence for DA receptor hypofunction in PFC in schizophrenia comes from several lines of research. There are decreased levels of DA metabolites in the cerebrospinal fluid of schizophrenic individuals, and these are correlated with poor working memory performance (134, 135). DA agonists may be able to ameliorate the patterns of activation in dlPFC during these tasks (136). Genetic variations of the COMT gene that cause increased metabolism of

DA are also associated with impaired PFC function, and a greater risk of schizophrenia (137). One post-mortem study of tyrosine hydroxylase immunolabeling showed differences in DA innervation of the dlPFC in patients (138), whereas postmortem studies of $D_1$Rs have not shown differences (139, 140). PET labeling studies of cortical $D_1$R density have not yielded consistent results (21, 141–143). More recently, Slifstein et al. (144) reported decreased amphetamine-induced DA release in the dlPFC in patients with schizophrenia, further supporting the hypothesis of cortical hypodopaminergia in this disorder. Thus, there is a major unmet need for the development of new psychopharmacologic agents for schizophrenia, in particular for cognitive deficits.

## Clinical studies of $D_1$ agonists

Single doses of the full $D_1$ agonist dihydrexidine have been given both to individuals with PD (92) and with schizophrenia (58, 94). In the schizophrenia study, patients were randomized in a cross-over design between dihydrexidine and placebo (58, 94). Side effects were minimal, no orthostatic changes were observed, and increased perfusion (i.e., via fMRI) in bilateral PFC was noted (58, 94), but with only a trend for improvements on the Controlled Oral Word Association Test or the Hopkins Verbal Learning Test. Another study used the mixed $D_2$:$D_1$ agonist pergolide in 25 subjects with schizotypal personality disorder and compared placebo and drug on neuropsychological performance (145). The pergolide group showed improvements in visual-spatial working memory, executive function, and verbal learning and memory, and suggested that drugs with $D_1$R properties may provide benefit for the cognitive abnormalities of schizophrenia spectrum disorders.

Because of the data on dlPFC hypofunction and $D_1$Rs, the effects of the active (+)-enantiomer (146) of dihydrexidine (numbered DAR-0100A) was studied as an add-on treatment for cognitive enhancement in schizophrenia. A PET receptor occupancy study in non-human primates using [$^{11}$C]NNC112 and [$^{11}$C]raclopride to examine $D_1$R and $D_2$R/$D_3$R, respectively, showed dose-dependent selective binding of DAR-0100A to the $D_1$R (147). A trial of 49 clinically stable individuals with schizophrenia involved three weeks of intermittent treatment with either placebo (normal saline), or a high (15 mg, the MTD) or low dose (0.5 mg) of DAR-0100A. These doses were chosen to avoid drug-induced hypotension (92). Because of the rapid metabolism in man (92), blood levels of DAR-0100A were below limits of quantification, suggesting that these doses of DAR-0100A achieved only minimal engagement of the $D_1$R, No treatment effects were found on BOLD fMRI signals during working memory tasks, on working memory domains of the MATRICS battery, or on clinical measures. Conversely, some improvement on the CogState Schizophrenia Battery was seen in the high dose group, as well as improvement in attention on the MATRICS battery in both treatment groups. Differences in patient population (especially medication status) may explain the more positive findings of Rosell et al. (95) who administered three 15 mg doses of DAR-0100A or placebo to 16 individuals with schizotypal personality disorder. Improvement was observed in working memory on the Paced Auditory Serial Audition Task (PASAT) and on the 2-Back to 0-back ratio, although this ratio was improved in part due to worse performance on the 0-back condition. Although these results are not totally conclusive, they suggest a pro-cognitive effect of a full $D_1$ agonist in schizophrenia. Importantly, that unquantifiable blood levels of DAR-0100A

(although nonspecific metabolites were qualitatively observed at levels commensurate with the two doses) were observed suggests that these doses of DAR-0100A achieved only minimal engagement of the $D_1$R, likely explaining these mixed results. These results certainly suggest studies of better $D_1$ agonists (i.e., that achieve more target engagement) are needed to more fully test the efficacy of this mechanism for cognitive enhancement in schizophrenia and reconcile the mixed findings from these trials.

## Future opportunities

As can be gleaned from the material above, one major goal should be the discovery of safe and highly bioavailable (probably non-catechol containing), full $D_1$ agonists. The accumulating evidence for a potential therapeutic role of $D_1$ agonists in several areas will hopefully spur both pharmaceutical companies and academic groups to jump existing hurdles. Patent activity suggests progress toward structurally novel agents, but none have been disclosed in the peer-reviewed literature at this time. There are, however, some alternate approaches that may be useful.

A $D_1$ positive allosteric modulator (PAM) would enhance the endogenous actions of DA at $D_1$R, and recently, the first published preclinical breakthrough in this area was reported for two series of PAMs (see Figure 4) that are active *in vitro* (148). One of the compounds was selective for $D_1$R, but had much lower activity at the murine vs. the human $D_1$R. A patent from Eli-Lilly also reports an additional chemotype for $D_1$ PAMs that potentiate relevant *in vivo* signals including locomotor activity and release of acetylcholine in PFC (149).

Another intriguing possibility is functionally selective $D_1$ ligands. As an example, in most assays, SKF-38393 is a partial agonist because it has much less intrinsic activity than DA or dihydrexidine. Consistent with classical pharmacology, this would explain why SKF-38393 is a much less effective antiparkinsonian drug than dihydrexidine. Yet in some systems, the two compounds are equally effective physiologically (75, 150). These data suggest that SKF-38393, while a partial agonist at most commonly tested $D_1$R mediated signaling pathways, may have higher intrinsic activity in others. There is significant functional selectivity even among experimental compounds considered “full agonists” (90, 91). Thus, discovery of new highly-biased $D_1$R ligands may be an important route to more selective actions *in vivo*, that also avoid problems like seizures and rapid tolerance.

Finally, to maximize the beneficial effects of $D_1$R stimulation on dlPFC function in schizophrenia will require addressing the “inverted U” dose-response curves seen *in vivo*. As noted earlier, one $D_1$R mechanism involves increased cAMP opening of HCN channels that can suppress all firing if doses are too high. Optimal effects on working memory can be achieved by careful dose titration, but this will be challenging because of inter-individual differences in drug metabolism and distribution. Besides a $D_1$R PAM or functionally selective $D_1$R orthosteric ligand, it may be that a $D_1$R selective compound with more “dopamine-like” affinity would be useful, as this might attenuate excessive cAMP-mediated opening of HCN channels. The potential for large effect sizes shown by existing data makes these challenges worthy of tackling.

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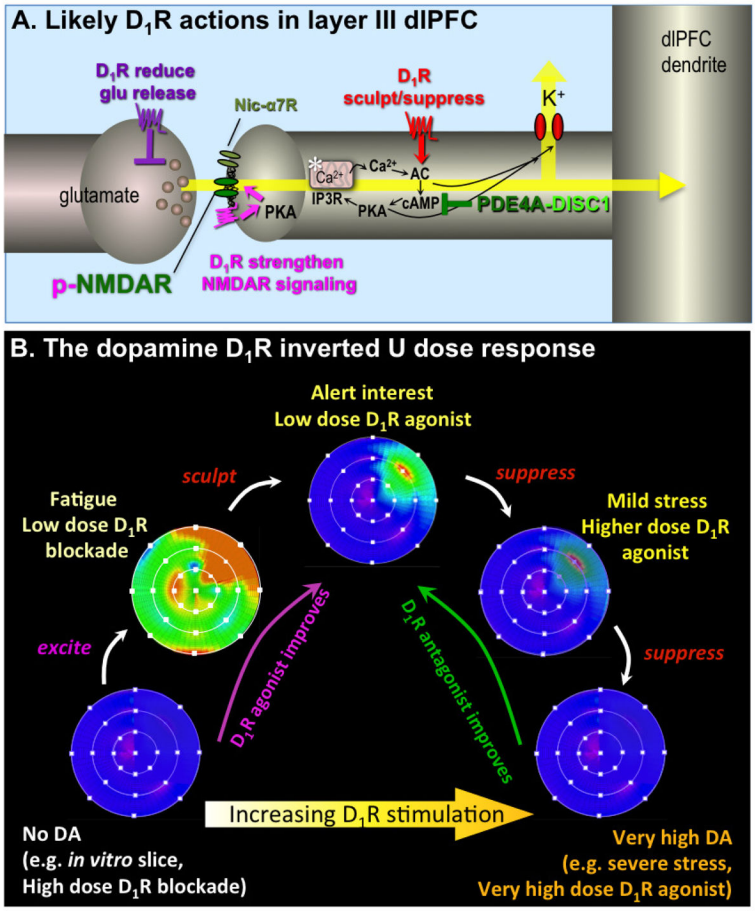


**Figure 1. Schematic illustration of DA $D_1$R influences on Delay cell firing in layer III of the primate dlPFC**

**A.** Localization of $D_1$R in layer III dlPFC pyramidal cell networks. Pyramidal cells interconnect via NMDAR synapses on spines, with permissive actions from nicotinic α7 receptors (nic- α7R). Immunoelectron microscopy has shown that $D_1$R are concentrated on dendritic spines, where they can be seen directly within the synapse (magenta), and near the synapse where they often co-localize with HCN or KCNQ potassium channels (red). The open state of both of these channels is increased by cAMP-PKA signaling. Physiological recordings from monkeys indicate that $D_1$R activates feedforward cAMP-PKA-calcium signaling, which opens $K^+$ channels and weakens nearby synaptic inputs (red). At optimal doses this sculpts away noise from irrelevant inputs, but at higher doses, e.g. as occurs during stress, it causes nonspecific suppression of Delay cell firing and loss of working memory. Feedforward cAMP-calcium signaling is held in check by the phosphodiesterase, PDE4A, which is anchored in place by DISC1 (Disrupted In Schizophrenia). Studies in nonprimate species suggest that $D_1$R within the synapse phosphorylate NMDAR via activation of cAMP-PKA and PKC signaling; this maintains NMDAR in the synaptic membrane and strengthens connections (magenta). There are also $D_1$R on glutamate axon terminals that may reduce glutamate release (purple). For detailed description, see Arnsten et al, 2015. The asterisk indicates the spine apparatus, the extension of the smooth endoplasmic reticulum into the spine.

**B.** A schematic illustration of the DA $D_1$R inverted U influence on the "memory fields" of dlPFC Delay cells. For details, see (5). Under optimal arousal conditions, Delay cells generate persistent representations of visual space, displaying high rates of firing (orange-red) to the memory of one spatial location, and low rates of firing (blue) to the memory of all other spatial locations. When there is no $D_1$R stimulation, Delay cells have little firing. Low levels of $D_1$R stimulation appear to be excitatory, e.g. phosphorylating NMDAR to increase their trafficking into the synapse (7). This can produce noisy firing for all directions, as represented by the generalized green-orange coloring of the memory field. With optimal levels of $D_1$R stimulation, there are additional sculpting actions, gating out "noise", e.g. by opening a subset of HCN channels. At still higher levels of $D_1$R stimulation (e.g. as occurs during stress), there is excessive HCN channel opening and Delay cell firing is generally suppressed. Under these conditions the neuron is not able to generate persistent representations of visual space.

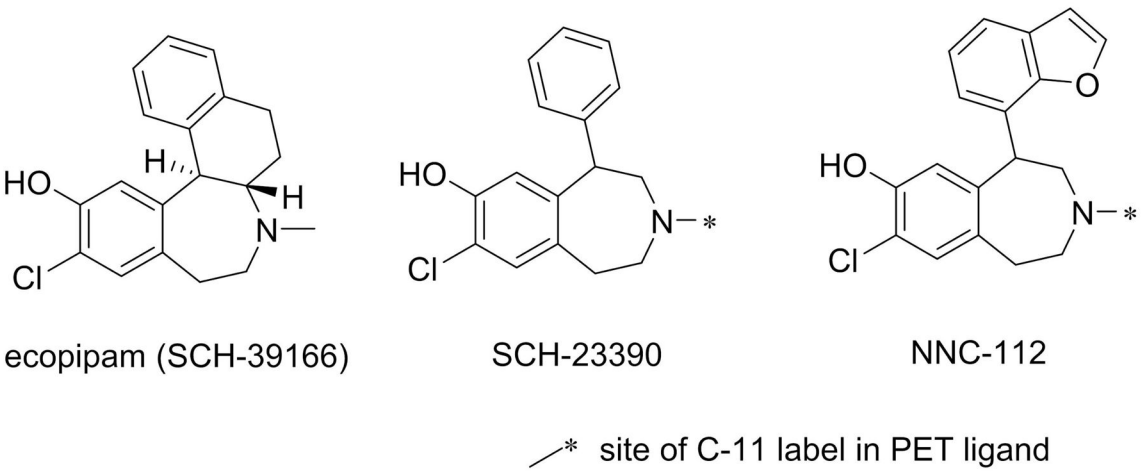


**Figure 2. Structures of selective $D_1$ antagonists and PET ligands**

The site of radiolabeling is shown by the asterisk. The most pharmacologically active isomer is shown, although these compounds are sometimes used as racemates.

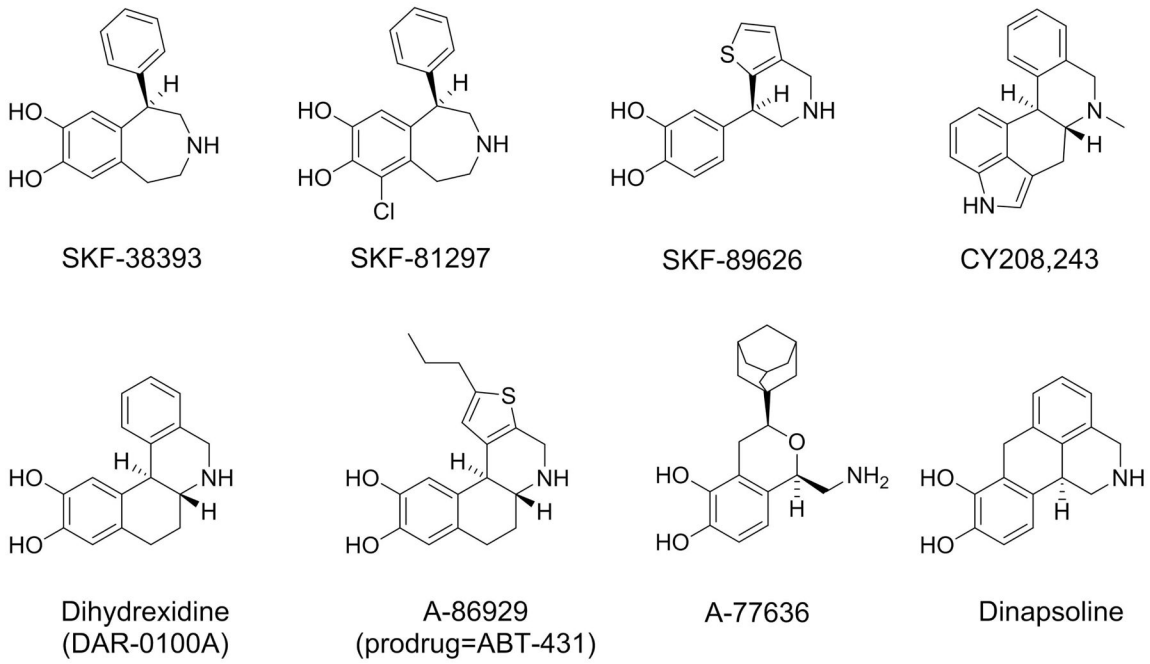


**Figure 3. Examples of important experimental $D_1$ agonists**

[Top Row] SKF-38393 (partial agonist) and SKF-82958 (full agonist) are phenylbenzazepines. SKF-89626 had higher intrinsic activity than SKF-38393, but lacked BBB permeability. CY208243 is a high $D_1$ intrinsic activity ergoline. [Bottom row] Four full $D_1$ agonists from four different chemotypes: A-77636, A-86829 (the active compound of the diacetyl prodrug ABT-431), dihydrexidine (DAR-0100A), and dinapsoline. The most pharmacologically active isomer is shown in all cases, although these compounds are sometimes used as racemates.

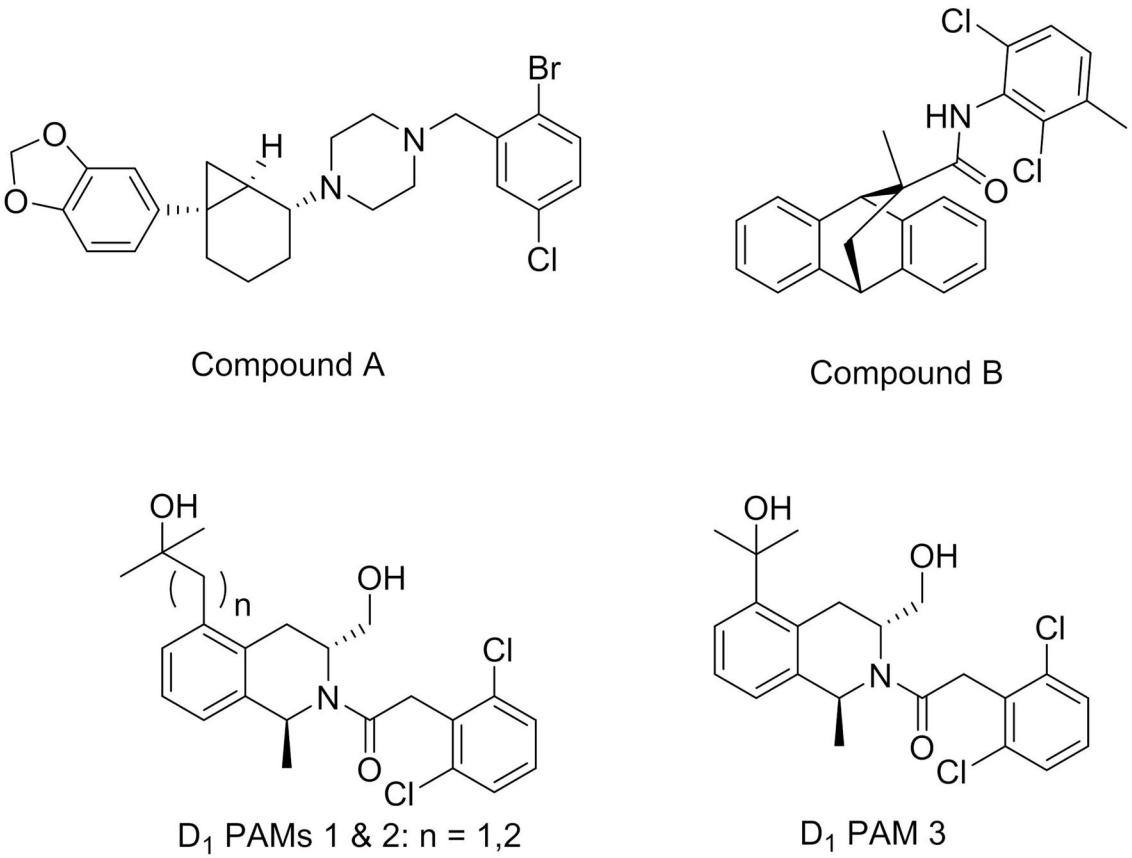


**Figure 4. Structures of $D_1$ positve allosteric modulators (PAMs)**

PAMs may offer an advantage over orthosteric (direct) agonists by interacting with endogenous dopamine tone, and as such, may possibly avoid biphasic effects currently seen with direct $D_1$ agonists.