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REVIEW

New therapeutic strategies targeting D1-type dopamine receptors for neuropsychiatric disease

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Abstract **The neurotransmitter dopamine acts via two major classes of receptors, D1-type and D2-type. D1 receptors are highly expressed in the striatum and can also be found in the cerebral cortex. Here we review the role of D1 dopamine signaling in two major domains: L-DOPA-induced dyskinesias in Parkinson's disease and cognition in neuropsychiatric disorders. While there are many drugs targeting D2-type receptors, there are no drugs that specifically target D1 receptors. It has been difficult to use selective D1-receptor agonists for clinical applications due to issues with bioavailability, binding affinity, pharmacological kinetics, and side effects. We propose potential therapies that selectively modulate D1 dopamine signaling by targeting second messengers downstream of D1 receptors, allosteric modulators, or by making targeted modifications to D1-receptor machinery. The development of therapies specific to D1-receptor signaling could be a new frontier in the treatment of neurological and psychiatric disorders.**

Keywords D1DR, dopamine D1 receptor, dyskinesia, cognition

Introduction

Dopamine is involved in motivation, movement, and cognition in the brain. It is a key neurotransmitter in Parkinson's disease (PD), schizophrenia, and addiction (Goldman-Rakic, 1998; Schultz, 2001). Dopaminergic neurons project from the ventral tegmental area and the substantia nigra to diverse brain areas including the striatum, amygdala, and cortex. Whereas the nigrostriatal pathway is primarily involved in the regulation and control of movement, mesocortical dopaminergic projections to the prefrontal cortex are implicated in cognitive processes such as attention and working memory (Goldman-Rakic et al., 2000). Both of these circuits malfunction in neurological and psychiatric diseases such as PD and schizophrenia. In this review we discuss D1 neurons and circuits, and highlight therapeutic opportunities targeting D1 dopamine receptors (D1DRs) in L-DOPA induced dyskinesia in PD and cognitive deficits in various neuropsychiatric diseases including schizophrenia, Alzheimer's disease, and Parkinson's disease.

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Dopamine receptors are broadly classified as D1-type and D2-type. These receptors are classified based on their biochemical actions on adenylyl cyclase, which regulates intracellular cAMP levels. Adenylyl cyclase can be positively or negatively modulated by G-proteins. D1-family (D1 and D5) receptors are coupled with a Gs/q-α subunit, while D2-family receptors (D2, D3, and D4) are coupled with a Gi-α subunit. D1DRs are exclusively expressed on postsynaptic neurons, while D2 dopamine receptors (D2DRs) are expressed on both presynaptic and postsynaptic neurons. D1/D2 receptor heteromers have been implicated in various pathology with unique signaling properties (Rashid et al., 2007; Perreault et al., 2011). Recent study suggest that D1/D2 dimers are either non-existent or non-detectable in adult rodent (Frederick et al., 2015). Dopamine receptors are found in many brain areas and peripheral tissues. D1DRs are densely expressed in the striatum, but are also expressed in the amygdala, olfactory bulb, cerebellum, and prefrontal cortex (Ariano and Sibley, 1994; Bergson et al., 1995). In the cerebral cortex, D1DRs are expressed on dendrites of pyramidal cells and on interneurons (Sesack et al., 2003). In the striatum, D1DRs are expressed on medium spiny neurons (MSNs). One challenge in localizing D1DRs is the lack of a highly specific antibody. However, transgenic techniques have assisted in this effort

(Lemberger et al., 2007; Calabresi et al., 2008; Gangarossa et al., 2012).

Dyskinesia

During the progression of PD, there is a substantial loss of dopaminergic input to the striatum. Dopamine replacement therapy with L-DOPA is the most widely-used and effective treatment for motor aspects of PD. However, up to 80% of patients develop L-DOPA-induced dyskinesias (LIDs) within 5–10 years of L-DOPA treatment. LIDs are severe and disruptive involuntary movements.

Dopamine acts in the striatum on MSNs, which make up 95% of the neurons in the striatum, and nearly 100% of the projection neurons. These neurons largely express either D1-type or D2-type dopamine receptors (Fig. 1). These distinct populations are expressed in two main output pathways: D1DRs in the striatonigral, or *direct* pathway, and D2DRs in the striatopallidal, or *indirect* pathway. Decreased signaling via both D1DRs and D2DRs slows and disorganizes movements (Jenner, 2008).

It is hypothesized that dopamine receptors become hypersensitive following the depletion of dopamine in the striatum (Calabresi et al., 2008). Although both the direct and indirect pathways are affected throughout the course of PD, previous work suggests the direct pathway involving D1DRs is preferentially involved in the development of LIDs. In MPTP-treated monkeys who develop LIDs D1DR mRNA is increased, while the same effect is not observed in monkeys without LIDs. These results suggest that chronic L-DOPA administration increases D1DR expression and D1 binding in the striatum (Aubert et al., 2005). The level of D1DR supersensitivity in these animals correlates positively with the severity of LIDs. Similarly, Hanrieder et al. (2011). demonstrated an increase in the proteins specifically expressed by D1 neurons, such as dynorphin B and substance P, in the striatum of rats with severe dyskinesias. Selective D1DR agonists have also been shown to lead to dyskinesias in rats, while D1DR antagonists, such as SCH23390, can mitigate the severity of LIDs in animal models (Taylor et al., 2005; Westin et al., 2007). Recent work by Darmopil et al. (2009) demonstrates that mice lacking the D1DR do not develop LIDs. Additionally, 6-hydroxydopamine (6-OHDA)-lesioned D1DR knockout mice do not have increased expression of FosB or dynorphinB in the striatum when compared to lesioned wild-type mice and D2DR knockout mice.

Adenylyl cyclase activity in D1DR MSNs is increased in response to dopaminergic stimulation in hemiparkinsonian rats (Taymans et al., 2005). Elevated levels of cAMP are also found in the striatum of PD patients (Pifl et al., 1992). In hemiparkinsonian rodents, the phosphorylation level of the dopamine- and cAMP-regulated phosphoprotein 32 kDa (DARPP-32) at Thr34 is dramatically elevated in the lesioned striatum in response to acute dopaminergic stimulation by L-DOPA. DARPP-32 is an important component of dopamine signaling, inhibiting the dephosphorylation of proteins which are phosphorylation targets of PKA, creating positive feedback for D1DR-mediated signaling as in Fig. 1 (Fienberg et al., 1998; Flores-Hernández et al., 2002). In MPTP-treated primates, dyskinesias are accompanied by increased expression of DARPP-32 and Cdk5. Interestingly, mice that exhibited more severe LIDs following chronic L-DOPA treatment expressed higher levels of phosphorylated DARPP-32 (Santini et al., 2007). Santini et al. (2007) also reported that DARPP-32 knockout mice manifest significantly lower LIDs when compared to wild-type mice. Stimulation of D1DRs enhances DARPP-32 phosphorylation at Thr34, and deactivation of DARPP-32 blunts D1-mediated signaling while suppressing D1 behavioral effects such as induced rotation (Fienberg et al., 1998).

The striatum receives glutamatergic input from the cortex and thalamus. The NMDA receptor antagonist, amantadine, has some anti-dyskinetic effects (Blanchet et al., 1998; Rodnitzky and Narayanan, 2014). It is postulated that D1DRs interact with NMDA receptors on MSNs and that PSD-95 expression can modulate D1DR expression (Fig.1) (Porras et al., 2012). In this study, authors found that PSD-95 expression was significantly higher in MPTP-treated monkeys and 6-OHDA-lesioned rats exhibiting LIDs. Additionally, they found that decreasing PSD-95 expression significantly reduced abnormal involuntary movement scores in the two animal models. These findings implicatethe expression of PSD-95 in the striatumas a novel target to reduce LIDs.

Though changes in the expression of both dopamine receptor types (D1- and D2-type) in the striatum have been reported (Guttman and Seeman, 1985; Pisani and Shen, 2009), changes in D1DR expression have been more consistent than those in the D2 receptor with LIDs. Together, these data support the hypothesis that D1DRs in the striatum are responsible for the development of LIDs. However, the role of D1 signaling on the neural activity of MSNs is unclear. Precisely understanding this relationship is key for titrating therapies for LID.

Cognition

Dopaminergic signaling also plays an important role in many aspects of cognition and is implicated in a variety of neurological disorders (Goldman-Rakic, 1998). People who suffer from diseases that affect the dopamine system (e.g. PD) can also be afflicted by cognitive deficits (Cools et al., 2001; Narayanan et al., 2013). The prefrontal cortex (PFC) is implicated in cognitive processes such as reasoning, planning, and spatial ability (Fuster, 2008). Furthermore, the PFC has many dopamine neurons and is sensitive to dopaminergic signaling (Cools et al., 2002). The PFC expresses more D1DRs than D2 receptors in rodents, primates, and humans

(Lidow et al., 1991; Hall et al., 1994; Santana et al., 2009). Because D1DRs are more abundant in the PFC, it has been suggested that the D1DRis involved in cognition. The role of D1DRs in cognition has been investigated in various imaging, pharmacological, genetic, and animal studies.

D1 agonists and antagonists in the PFC significantly affect executive functions such as working memory. Prefrontal dopamine levels are elevated in delayed-response working memory tasks but not in non-delayed tasks (Watanabe et al., 1997; Phillips et al., 2004; Rossetti and Carboni, 2005). Indeed, primates performing an oculomotor delayed-response task were impaired by lateral PFC infusions of D1 antagonists (Sawaguchi and Goldman-Rakic, 1991; Sawaguchi and Goldman-Rakic, 1994); however, motor functions were not affected. D1 antagonists also specifically impaired mnemonic information encoded by single PFC neurons (Williams and Goldman-Rakic, 1995). Low levels of PFC D1DR agonists can enhance working memory performance (Vijayraghavan et al., 2007), particularly in older primates (Castner and Goldman-Rakic, 2004) or in patients taking antipsychotics (Castner et al., 2000). However, higher levels of D1DR agonists impair memory performance (Zahrt et al., 1997; Vijayraghavan et al., 2007). D1 signaling is also involved in elementary cognitive processing such as interval timing (Narayanan et al., 2012) and temporal processing during reaction time tasks (Parker et al., 2013a). Focal blockade of D1 dopamine receptors diminishes 'ramping' neuronal activity that increases or decreases spiking activity until interval end (Parker et al., 2014). Furthermore, D1 blockade also attenuates theta rhythms in mid-frontal cortex that are a mechanism for cognitive control (Cavanagh and Frank, 2014; Parker et al., 2014). Taken together, these data firmly implicate prefrontal D1 signaling in cognitive processing (Goldman-Rakic et al., 2000; Goldman-Rakic et al., 2004).

Dopamine is released in the PFC when appetitive and aversive events occur (Schultz, 1997; Ungless et al., 2004; Narayanan et al., 2010; Land et al., 2014). An optimal level of D1 activation may increase the signal to noise ratio to improve the efficiency of these networks. Dopamine neurons predominantly exhibit two firing patterns, tonic and phasic (Grace et al., 2007). Tonic activity refers to neural activity at a relatively constant rate; whereas phasic activity is characterized by brief increases in firing of dopamine neurons associated with reward-predictive stimuli. Such phasic bursts of activity can potently and precisely affect post-synaptic networks (Lapish et al., 2007). Cortical dopamine systems are involved in various types of learning. Robust and sustained elevation ofdopamine levels are observed with classical appetitive or aversive conditioning to a context (Yoshioka et al., 1996; Feenstra et al., 1999) or to an auditory cue (Wilkinson et al., 1998; Feenstra et al., 2001).

Several investigators have suggested that D1DRs are tuned to an inverted U dose–response curve (Cools and D'Esposito, 2011). According to this model, both too much and too little dopamine or D1 activation can impair cognitive performance. Using positron emission tomography (PET), Takahashi et al. (2008) found an inverted U-shaped relationship in healthy subjects between PFC D1DR binding and performance on the Wisconsin Card Sorting Test. An inverted U-shaped relationship between D1DR activation and performance has been found in working memory using pharmacological manipulation. As discussed above, D1DR agonists led to impairments in a spatial working memory task, but failed to do so at low doses. Performance was also impaired with high doses of a D1DR antagonist (Vijayraghavan et al., 2007). These results suggest that D1DRs need to function at an optimal level, as too little or too much activation of the receptors leads to cognitive impairment. The inverted U-shaped relationship between D1DR activity and cognitive performance can also be found at the molecular level. The inverted-U hypothesis is also evident in the PFC following moderate administration of the D1DR antagonist (SCH39166). Pyramidal cells that were selective to a response increased firing, whereas higher doses of antagonist abolished this effect (Williams and Goldman-Rakic, 1995). However, it is still not clear how these receptor dynamics influence prefrontal network function.

In schizophrenia, antidopaminergic drugs have been used for over 50 years. The traditional dopamine hypothesis postulated that the positive symptoms of schizophrenia resulted from hyperactive dopaminergic signaling. This idea has been partially supported by the ability of drugs to blocking D2 receptors and mitigate the psychotic symptoms (Seeman et al., 1975; Creese et al., 1976; Seeman, 1987). Based on these early data, much of the effort in antipsychotic drug development has been focused on antagonizing D2 receptors. Although D1 and D2 receptors are generally not found on the same neurons, the activation of D1DRs can enhance the stereotyped D2-mediated behavioral responses (LaHoste et al., 2000).

Selective D1DR antagonists have not shown efficacy in treating schizophrenia and may actually exacerbate tardive dyskinesia (Karlsson et al., 1995). On the other hand, partial D1 antagonists such as clozapine are highly effective and can improve cognition in schizophrenia (Hagger et al., 1993). Clozapine is also useful for psychosis in Parkinson's disease (Friedman and Lannon, 1989). However, clozapine is not a selective pharmaceutical agent binding to many other receptors and is challenging to use clinically because of dose-limiting side effects (Klein et al., 2003). Other currently approved antipsychotics act partially on D2 receptors in combination with serotonin and norepinephrine, suggesting that DA system is critical in modulating positive symptoms (Mailman and Murthy, 2010). The combination of a D1 agonist and D2 antagonist or other functionally selective drugs may be one route to effective next-generation therapies.

Using PET, Pizzolato et al. (1996) showed that D2-receptor binding was significantly reduced in Alzheimer's disease patients without overt extra-pyramidal symptoms such as tremor, akathesia, dystonia and anxiety. However,

Kemppainen et al. (2000) presented conflicting evidence that D1-, but not D2-, receptor binding in the putamen and caudate nucleus was decreased in Alzheimer's disease patients. No significant association was observed between cognitive deficits and the binding density of dopamine D1/D2 receptors in the putamen and caudate nucleus. Taken together, it seems the reduction of dopamine receptors was positively correlated with severity of cognitive dysfunction in Alzheimer's disease patients.

Mattila et al. (2001) observed that the decrease in the density of D1DRs in the caudate nucleus and putamen of PD patients was associated with cognitive decline as measured by Reisberg's global deterioration scale. To investigate the correlation of working memory decline with D1DR density in PD patients, Costa et al. (2009) treated PD patients with the D1DR agonist pergolide. They found a clear improvement in working memory function, indicating the importance of D1DR modulation in frontal-striatal circuits. Although clozapine is helpful in psychotic symptoms of schizophrenia, small-scale studies did not identify a clear benefit in executive tasks such as working memory (Hagger et al., 1993; Green and Harvey, 2014). In a randomized prospective multi-center study, Rektorová et al. (2005) indicated that dopamine D1- and D2-receptor agonists displayed positive effects on cognitive dysfunction in advanced PD patients.

The role of dopamine receptor-mediated signaling pathways in cognitive dysfunction in PD are well recognized (Narayanan et al., 2013; Parker et al., 2013b). It has become increasingly apparent that dopamine receptor-mediated signaling cascades are altered as a consequence of dopaminergic denervation in PD and that the functional reactions of dopamine receptors may result from a variety of changes in the signaling mechanisms. The simultaneous activation of the D2 receptor suppresses transmembrane Ca^{2+} currents, activating phospholipase C and calcium-dependent phosphatase calcineurin (Hernandez-Lopez et al., 2000). After the denervation of nigrostriatal dopaminergic neurons, ERK1/2/MAP kinase (extracellular signal-regulated kinase/mitogen-activated protein kinase) was activated in response to D1DR agonists, either alone or in combination with the stimulation of corticostriatal afferents (Gerfen et al., 2002). These studies suggest that not only dopamine receptors, but also downstream signaling molecules such as ERKs and MAP kinase, maybe future targets for cognitive symptoms of neuropsychiatric diseases.

Abnormal neurotransmission in the dopamine and glutamate (NMDA) systems plays a critical role in the pathophysiology of schizophrenia. The hyperactivity of dopamine in subcortical structures is thought to be associated with the positive symptoms of the disease, whereas D1DR hypoactivity in the frontal cortex has recently been connected to the negative symptoms and impaired cognitive function (Arnsten et al., 1994). Low doses of selective D1DR agonists (e.g., DHX, A77636, and SKF-81297) enhance cognitive function in primates (Roberts et al., 2010).

Challenges and new directions

Drugs that target the dopaminergic system are widely used for treating psychiatric disorders, such as D2DR antagonists for schizophrenia and L-DOPA for PD. These drugs have pharmacokinetic problems including bioavailability and specificity to target individual receptors (Khor and Hsu, 2007). D1DR drugs can have short half-lives and complex pharmaco dynamics, even when intracranially infused (Sawaguchi and Goldman-Rakic, 1994). D1 receptors are likely oligomers (Lee et al., 2000), and receptor dynamics are influenced by PSD-95 (Sun et al., 2009; Ha et al., 2012). D1DR kinetics may also influence phenomena such as LIDs (Berthet et al., 2009).

Combined activation of D1DRs and nicotinic receptors may be another promising therapeutic avenue for improving cognitive deficits and negative symptoms in schizophrenia. Recent studies have provided a wealth of information on the structure-activity relationship of the D1DR (Charifson et al., 1989; Hoffman et al., 1999; Neumeyer et al., 2003). However, a lack of information on the exact three-dimensional orientation of amino acid residues at the binding sites of the dopamine receptors, together with the limited understanding of interactions between the D1DR and selective ligands, still hinders the rational design and development of potent and selective D1 receptor agents. Based on these data, there are three new directions that could be pursued: 1) screening existing drug libraries for new D1 drugs, 2) novel genetic methods targeting D1DRs, and 3) optogenetic or electrical methods of stimulating D1 circuits.

Allosteric modulators are another potential therapeutic avenue. Allosteric modulators bind to a distinct site on the receptor other than it's active site, and in the case of the dopamine receptors, can potently influence its pharmokinetics site (Hoare et al., 2000; Soriano et al., 2010). These modulators have the potential to be highly selective and reversible (Fawzi et al., 2001). Drugs that are allosteric modulators of D1 or D2 receptors may be a further target pursued by future therapies.

Many drugs that manipulate D1DRs exist and are available for preclinical work. However, there have been few ongoing clinical trials for D1DR drugs in schizophrenia or for LIDs. Drug screens of existing compound libraries are likely to identify more of these drugs. This may be the most immediate avenue for drugs targeting D1DRs. Of note, both specific D1DRs and drugs with complex receptor profiles, such as clozapine, could be tested for both cognitive and LID indications.

The recombinant adeno-associated virus (AAV) vectors are excellent tools for gene therapy in the treatment of neuropsychiatric diseases. While gene therapy is still in early phases of testing, it has an excellent safety profile. PD patients are excellent candidates for gene therapy, particularly since major symptoms in PD are caused by the degeneration

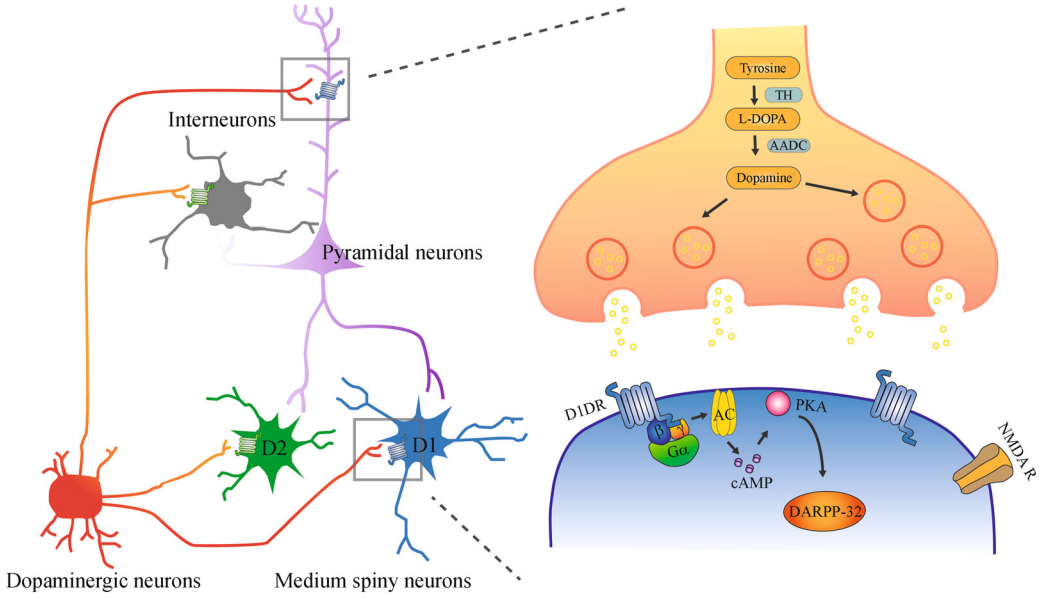

Figure 1 Schematic diagram shows projections of midbrain dopaminergic projections (ventral tegmental area or substantia nigra) to the frontal cortex and striatum and intracellular signaling pathway in a D1 receptor synapse. Midbrain dopaminergic neurons (red) project to both glutamatergic pyramidal neurons (purple) and GABAergic interneurons (gray) in prefrontal cortex. Some midbrain dopaminergic neurons project to medium spiny neurons in the striatum that express either D1 dopamine receptors (blue) or D2 dopamine receptors (green). Dopamine synthesis in dopaminergic neurons requires two key proteins, tyrosine hydroxylase (TH) and aromatic L-amino acid decarboxylase (AADC), which are target molecules for dopaminergic degenerating diseases (PD). D1DRs in post-synaptic neurons are coupled with G-proteins. Activation of D1DRs stimulates adenylate cyclase (AC) which results in increased cAMP levels. Increasing PKA activity with cAMP changes subsequently induces phosphorylation of DARPP-32.

of specific populations of dopaminergic neurons. Clinical trials with gene therapy suggest that both AAV and lentivirus-based vectors are safe for human clinical application (LeWitt et al., 2011; Bartus et al., 2013). This technology raises the possibility of locally introducing specific modifications to the D1 receptor for neuropsychiatric diseases.

Recent advances in optogenetic techniques have made significant progress in elucidating the role of D1DRs in neurological disorders (Shuen et al., 2008; Narayanan et al., 2012; Cui et al., 2013; Land et al., 2014). Optogenetic techniques have unique advantages over traditional approaches. The light-sensitive channels change firing patterns in response to specific spectrums of light at very high temporal resolution (Boyden et al., 2005; Carter and de Lecea, 2011). Bilateral optogenetic activation of D1 neurons in the dorsal striatum increased fine movement and ambulation time in freely-moving animals (Kravitz et al., 2010). Narayanan et al. (2012) showed that optogenetic stimulation of D1 neurons in the PFC can enhance temporal control in an interval-timing task. Optogenetic stimulation of D1 neurons in the PFC increases food intake (Land et al., 2014). These studies suggest that optogenetic techniques could provide high-fidelity manipulations of PFC circuits in cognition.

Although these findings may be clinically relevant, optogenetic fiber optics are still too invasive for human use. A designer receptor exclusively activated by designer drug (DREADD) may be better-suited for the manipulation of neuronal activity in a target brain area (Farrell et al., 2013). Kätzel et al. (2014) showed that modified muscarinic receptor hM4Di activation with clozapine N-oxide successfully attenuated chronic focal neocortical seizures in a rat model. These results provide novel treatment options for on-demand seizure reduction. A similar approach may also be possible for other neurological disorders such as schizophrenia or PD. The role D1DRs in the PFC play in cognitive function is well established. Thus, these circuits are possible targets for optogenetics, gene therapy, and DREADDs. These techniques have the potential to elucidate the activity-dependent effects of disordered circuits in translationally relevant animal models. Manipulation of D1 neuronal circuits requires accurate control of activity due to the inverted U-shaped relationship between prefrontal D1DRs and cognitive function.

Overall, advancements in viral vector-based gene therapy could provide new possibilities for treatments. While there are many obstacles to overcome, these novel treatments have distinct advantages over traditional drug-based treatments. Optogenetics and DREADD can facilitate studying D1 circuits and molecular mechanisms in LIDs or cognition with specificity. We are hopeful that these efforts will lead to new therapies targeting D1DRs in human disease.

Compliance with ethics guidelines

Young-Cho Kim, Stephanie L. Alberico, Eric Emmons, and Nandakumar S. Narayanan declare that they have no conflict of

interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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