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Dopamine D3 receptor: a neglected participant in Parkinson Disease pathogenesis and treatment?

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Abstract

Parkinson disease (PD) is a neurodegenerative disorder characterized by motor and non-motor symptoms which relentlessly and progressively lead to substantial disability and economic burden. Pathologically, these symptoms follow the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) associated with abnormal α-synuclein (α-Syn) deposition as cytoplasmic inclusions called Lewy bodies in pigmented brainstem nuclei, and in dystrophic neurons in striatal and cortical regions (Lewy neurites). Pharmacotherapy for PD focuses on improving quality of life and primarily targets dopaminergic pathways. Dopamine acts through two families of receptors, dopamine D1-like and dopamine D2-like; dopamine D3 receptors (D3R) belong to dopamine D2 receptor (D2R) family. Although D3R's precise role in the pathophysiology and treatment of PD has not been determined, we present evidence suggesting an important role for D3R in the early development and occurrence of PD. Agonist activation of D3R increases dopamine concentration, decreases α-Syn accumulation, enhances secretion of brain derived neurotrophic factors (BDNF), ameliorates neuroinflammation, alleviates oxidative stress, promotes neurogenesis in the nigrostriatal pathway, interacts with D1R to reduce PD associated motor symptoms and ameliorates side effects of levodopa (L-DOPA) treatment. Furthermore, D3R mutations can predict

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PD age of onset and prognosis of PD treatment. The role of D3R in PD merits further research. This review elucidates the potential role of D3R in PD pathogenesis and therapy.

Keywords

Dopamine D3 receptor; Parkinson disease; α-synuclein; BDNF; neuroinflammation

1 Introduction

Parkinson disease (PD), the second most common progressive neurodegenerative disorder, affects ~1% population over 60 years old (Macdonald et al., 2018), and is characterized by resting tremor, bradykinesia, rigidity and postural instability (Kalia and Lang, 2015). PD is typically not diagnosed until motor symptoms develop, although non-motor manifestations including depression, sleep problems and loss of smell, typically begin years earlier (Srivanitchapoom et al., 2018). Current treatment focuses on relief of motor symptoms and no approved treatment slows disease progression. Ideally, disease modifying interventions should be applied as early as possible. While most pharmacotherapies have focused on dopamine D1 receptor (D1R) and dopamine D2 receptor (D2R) (Lewis et al., 2006), the stimulation in D3R plays an important role in PD pathogenesis. Thus, D3R may both provide a biomarker for early-stage pathological changes and also represent a target for development of novel therapeutics. In this communication we review the characteristics of D3R, its role in the pathogenesis of PD and as a potential target for therapeutics.

Dopamine (3-hydroxytyramine, DA) plays a critical part in movement, cognition, emotion, memory, reward, and drug addiction, and involves in a number of distinct neurodegenerative diseases, in which PD is the most widely recognized. Early motor manifestations of PD result from degeneration of nigral dopaminergic cell bodies in the substantia nigra pars compacta (SNpc) and the subsequent dysfunction of the terminal fields of those neurons producing a reduction in striatal DA (Girault and Greengard, 2004). DA binds to five closely related yet functionally distinct G protein-coupled receptors (GPCRs) named dopamine receptors (DRs). These DRs are divided into two major groups: the D1-like receptors (D1, D5), and the D2-like receptors (D2, D3, D4). It is commonly believed that D1Rs couple to $G\alpha_{s/olf}$ if and induce production of cyclic adenosine monophosphate (cAMP) and the activation of protein kinase A (PKA), while D2Rs activate $G\alpha_{i/o}$ and inhibit cAMP production (Beaulieu and Gainetdinov, 2011). These receptors differ in their distribution, expression, affinity and functional properties (see Table 1).

DA can not cross the blood brain barrier, so the prodrug levodopa (L-DOPA) was administered to patients with PD. This therapeutic approach provided dramatic clinical benefit but motor complications like “on-off’ fluctuations soon limited its clinical application (Wijeyekoon and Barker, 2009). Subsequently, DR agonists were developed but these agonists were non-selective or selective only for D1Rs or D2Rs families (Hori and Kunugi, 2013; Moore et al., 2014). DR agonist therapy is more prone to produce non-motor side effects that include neuropsychiatric problems such as hallucinations, delusions, impulse control disorders (ICD), cognitive impairment and non-neuropsychiatric problems

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such as gastrointestinal symptoms, orthostatic hypotension and valvular heart diseases (Brusa et al., 2003; Fenelon et al., 2000; Hori and Kunugi, 2013; Lang, 2001; Poewe, 2003; Voon et al., 2011). Some of these side effects are related to the lack of subtype specificity. Unfortunately, high amino acid sequence homogeneity across DR subtypes creates challenges in developing subtype selective agonists.

Although many studies have focused on D1R and D2R specific drugs for PD, D3R may be an appropriate alternative target. Evidence supporting this strategy comes from: 1.) Although the density of D1R and D2R are 2~3 times higher than D3R density in the striatum of aged human brain (Sun et al., 2012), DA binds to D3R with more than 100-fold higher affinity than it binds to D2R or D1R. Furthermore, therapeutic activation of D3R may be highly relevant since the basal concentrations of DA in extracellular (5-10 nM) and synaptic (50 nM) spaces (Prieto, 2017) are much lower than the K_i of DA at D1R or D2R, but higher than its K_i at D3R (see Table 1); 2.) Among all classes of pharmacological drugs that have been evaluated, D2R/D3R agonists are considered to be the most effective treatment for motor deficits in PD (Magnard et al., 2016). However, due to the lack of clearly defined subtype-selective therapeutics, it is hard to clarify which DR subtype is responsible for beneficial effects when treating patients with PD (Magnard et al., 2016). Pramipexole, apomorphine, ropinirole and rotigotine are currently the most commonly used DA agonists. Pramipexole, which was thought to be a D1R&D2R receptor agonist in 1990 (Kaneko et al., 1990), was later found to be a potent D3R agonist (Chen et al., 2014) and preferentially stimulates D3R compared with D2R (D2R/D3R selectivity of 24-800) (Cortes et al., 2016) with little affinity (>1000 nM) to D1R (Wood et al., 2015). Apomorphine, ropinirole and rotigotine, first reported as D2R agonists (Eden et al., 1990; Umegaki et al., 1997; Van der Weide et al., 1988), were found to bind to D3R with 2~4, 19~94 and 19~20 fold higher affinity than D2R (reviewed in (Cortes et al., 2016)). Thus D3R action of these drugs may be more important than initially expected, and early studies should be reevaluated.

D3R was firstly discovered in 1990 (Sokoloff et al., 1990), but initial researches into its action were hampered due to lack of potent and selective D3R ligands. D3R belongs to the D2R family and possesses seven membrane spanning-helices, an intercellular carboxyl terminus, and an extracellular amino terminus linked with intra and extra-cellular protein loops (Maramai et al., 2016). D3R is both a presynaptic autoreceptor and a postsynaptic receptor, distinguishing it from most of other DR types except D2R (see Table 1). Studies indicate that D3R plays an important role in in the CNS by modulating motor activity, emotions, memory and reward mechanisms (Beaulieu and Gainetdinov, 2011), thus D3R therapies initially focused on schizophrenia and drug addiction. Recent studies have addressed the potential involvement of D3R in PD. Here we review the role of D3Rin the pathogenesis, treatment and prognosis of PD and potential mechanisms underlying its role in treatment of PD.

2 The D3R regulation in the nigrostriatal regions of PD

2.1 The importance of biomarkers in PD pathogenesis

PD is pathologically defined post-mortem by abnormal α-synuclein (α-Syn) deposition (Lewy bodies/neurites) in the SNpc, striatal, and cortical regions, as well as a marked loss of

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dopamine projection from SN to striatum (Dauer and Przedborski, 2003; Zhang et al., 2018). The development of therapies for PD is limited by lacking in objective markers that show the pathogenesis and severity of PD. Pathologically, α-Syn is closely related to PD and considerable research efforts were made to find a suitable biomarker for α-Syn. However, no *in vivo* imaging biomarkers of α-Syn deposition are currently available. Thus, detection of α-Syn concentration in bodily fluid is used to evaluate if they are related to the progression of PD(Fayyad et al., 2019). Blood is the most accessible bodily fluid but the detection α-Syn in blood has yielded inconsistent results. Blood tests have given both increased (Miller et al., 2004) and decreased α-Syn levels (Li et al., 2007) in PD patients when compared with controls. Most of the results using cerebrospinal fluid (CSF) have shown that total α-Syn is down-regulated in PD (Fayyad et al., 2019), except one reported no differences between PD and control cohorts (Ohrfelt et al., 2009). However, this is a difficult method to apply clinically, because cerebrospinal fluid is obtained by lumbar puncture which is especially hard for elderly PD patients. As a result, researchers have turned their attention toward tracers, which can detect the release (via DAT and VMAT) and activation (DRs) of dopamine. The measures of SN uptake of [^{11}C]DTBZ, a marker for vesicular monoamine transporter type 2 (VMAT2), and [11C]CFT, a marker for dopamine active transporter (DAT), do correlate with nigral cell counts throughout the full range of nigral cell loss (Tabbal et al., 2012). These findings are consistent with a postmortem study of PD that demonstrated a flooring effect of presynaptic dopaminergic measures in patients with moderate disease (Kordower et al., 2013) and in a longitudinal PET study in people with PD (Kuramoto et al., 2013). However, as we mentioned earlier, no tracers can accurately detect D2R or D3R because of the high structural similarity between die two receptors.

2.2 Quantitative autoradiography assay for measuring D2R and D3R densities

We developed a quantitative autoradiography based mathematical model for calculating the absolute densities of D2R and D3R using *in vitro* binding data obtained from D3R preferring antagonist [^{3}H]WC-10 (Xu et al., 2009) and D2R preferring antagonist [^{3}H]raclopride (Xu et al., 2010). [^{3}H]WC-10 and [^{3}H]raclopride bind to D2R and D3R with different labeling proportions. The specific bound amount of receptors of single concentration of [^{3}H]WC-10 or [^{3}H]raclopride binding can be expressed by the formulas:

$$[^3\text{H}]\text{WC}-10: a_1D_2 + b_1D_3 = B_1 \qquad [^3\text{H}]\text{raclopride}: a_2D_2 + b_2D_3 = B_2,$$

Where a_1 and b_1 are the fractional occupancies of [^{3}H]WC-10 to D2R and D3R; B_1 is the apparent receptor binding density (D_2+D_3) directly measured from autoradiography studies of [^{3}H]WC-10; a_2, b_2, and B_2 are the same parameters for [^{3}H]raclopride; D_2, D_3 are the absolute densities of D2R and D3R. The absolute densities of D2R and D3R were calculated by solving the simultaneous equations:

$$D_2 = \frac{b_2B_1 - b_1B_2}{a_1b_2 - a_2b_1} \qquad D_3 = \frac{a_1B_2 - a_2B_1}{a_1b_2 - a_2b_1}$$

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This novel assay has been used for evaluating DR subtypes alterations in mouse models of sleep deprivation and attention deficiency (Brown et al., 2011; Lim et al., 2011), and genetic PD models including DJ-1 and Pink-1 knockout (KO) rats (Sun et al., 2013b). The first comprehensive analysis of presynaptic (VMAT2 and DAT) and postsynaptic (DR) biomarkers in the striatal and extrastriatal regions was conducted in aged human brains (Sun et al., 2012). The differential distribution and reported density of D1R, D2R, D3R, DAT and VMAT2 are shown in Figure 1 (Sun et al., 2012). D3R was upregulated, whereas D1R and D2R were not, in striatum and downregulated in SN in PD dementia brains. The observed increase in striatal D3R may reflect a compensatory change upon dopaminergic denervation, while the reduction of nigral D3R density reflects neuronal loss in the nigrostriatal system in PD with dementia (Sun et al., 2013a).

3 The change of D3R expression in preclinical or prodromal stage of PD

Due to limitations in ligand selectivity, although several early studies used nonselective D2R/D3R ligands which indicated a potential role of D2R in PD, the potential influence of D3R in PD pathogenesis cannot be excluded. For example, studies using raclopride and fallypride demonstrated that D2R density increase in the striatum of early-stage PD patients (Fisher et al., 2013; Rinne et al., 1995). Another study, using raclopride, showed that there was increased binding of D2R/D3R in the early symptomatic stage of MPTP-intoxicated monkey model (Ballanger et al., 2016). However, both raclopride and fallypride do not differentiate between D2R and D3R (Le Foll et al., 2014b; Mukherjee et al., 2015). One research also proved that it is the D3R, rather than D2R mediated modulation was enhanced to induce Ca^{2+} current and synaptic GABA release in striatal neurons after DA depletion which mimics the early pathological feature of PD in an *in vitro* study (Prieto et al., 2011).

Why D3R is increased in the early stage of PD? Increased D3R promotes T-cell activation and induces neuroinflammation, which may underlie the role D3R activation plays in PD pathogenesis. The activation of D3R on the surface of T-cells reduces cAMP levels and extracellular regulated protein kinases 2 (ERK2)-phosphorylation, increases proliferation and adhesion of T-cells, enhances CD4+ T-cell activation(Franz et al., 2015), further attenuates T-helper 2 (Th2) differentiation, and promotes Th1 responses by regulating cytokine signaling 5, a negative regulator of Th2 development (Pacheco, 2017). The activation of D3R produces changes in T cells that eventually leads to their ability to cross the BBB, changes in their cytokine profile, increases in inflammatory cells, and aggravates inflammatory response (Ilani et al., 2004). This phenomenon may play a critical role in PD pathogenesis as the CD4+ T-cells obtained from PD patients have higher Th1-biased differentiation than those obtained from healthy control, which lead to 2 fold higher frequency of Th1 cells in PD individuals than in healthy control (Elgueta et al., 2019). It has also been observed that the T-cells with higher densities of D3R infiltrate through the BBB and into the SN and induce the activation of microglia (Gonzalez et al., 2013), resulting in the production of more inflammatory factors when compared with D3R−/− counterparts (Xue et al., 2016). Activated microglia further induce neuroinflammation and subsequent neurodegeneration of DAergic neurons in the SN - one of the main pathological characteristics of PD (Elgueta et al., 2019). One study of note, directly correlate, the expression of D3R in peripheral blood correlated with neuroinflammation in the CNS,

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degeneration of DAergic neurons in SN, and the occurrence of PD. In this instance, RAG1 KO mice - which lack T-cells - were resistant to MPTP-induced neurodegeneration. However, after these mice were reconstituted with wild-type CD4+ T-cells, they were susceptible to MPTP-induced DAergic neuronal damage. In contrast, RAG1 mice that were administrated $D3R^{-/-}$ CD4+ T-cells were completely refractory to neuroinflammation and consequent neurodegeneration (Gonzalez et al., 2013).

Therefore, it was proposed that high expression of D3R mRNA in the blood be considered as the disease specific biomarker during the preclinical stage of PD. A research observed the change of D3R mRNA blood cells of MPTP-treated mice at the presymptomatic stage. The results showed that D3R mRNA was enhanced in the mice at the presymptomatic PD stage, however decreased at the symptomatic PD stage (Kim et al., 2018). All mice in the study eventually showed significant decrease of DA content in the striatum at the symptomatic stage (Kim et al., 2018). Thus, Inhibition of D3R prior to the onset of clinical conditions may hinder the pathogenesis of PD. One research showed that before the administration of MPTP, which implies the pathogenesis of PD, injection with D3R selective antagonist PG01037 or using $D3R^{-/-}$ mice could completely reverse neuroinflammation and consequent neurodegeneration, thus eliminate parkinsonian symptoms (Elgueta et al., 2017).

However, the evidence for a protective role of D3R inhibition in mitigating PD pathogenesis is not completely consistent. There is a common notion that chronic tobacco use is associated with a lower risk for PD. Researchers observed that nicotine induced D3R activation to help signaling structural plasticity in mesencephalic DAergic neurons (Collo et al., 2013). Moreover, another study proposed that this stimulation of D3R by nicotine induced D3R-nAChR heteromer activation that attenuated α-syn aggregation (Bono et al., 2019). In addition, others reported a significant decrease of D3R mRNA expression in peripheral blood lymphocytes (PBLs) of PD patients compared with healthy controls (Gui et al., 2011). These studies suggests conflicting conclusions; either a decreased density of D3R or the inactivation of D3R is an indication of the early stage of PD.

There are many factors that may be influencing the inconsistent results in this line of research. First, there is a possibility that a high density of D3Rs may reflect a compensatory mechanism, common for many receptors, due to the dopamine depletions or inactivation of D3R. Thus, the increased D3R expression in early PD and the treatment of diagnosed PD with D3R agonists are not contradictive. Second, it has been suggested that although D3R densities are observed to change, it is actually the ratio of D3R to related neuroreceptors that is associated with the onset of PD. Animal model studies have shown that the continuous increase in the D1R/D3R ratio may be a physiological basis of PD among middle-aged and elderly populations (Keeler et al., 2016). Third, in recent years there has been a focus on the relationship between D3R polymorphism and PD pathogenesis. A study evaluating the association between the polymorphisms of D2R and D3R genes (D2R: rs1800497, rs1079597, rs6278, rs6279, rs273482, rs1799732 and rs1076563; D3R: rs6280 and rs2134655) and their influence in PD pathogenesis was conducted among 4279 PD cases and 5661 controls. The results showed a significant association between PD occurrence and D3Rrs2134655 polymorphism (Dai et al., 2014). Another study discussing the relationship between D3R polymorphisms and the age of PD occurrence showed that D3R

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polymorphism (rs6280), rather than D2R (Taq 1A, rs1800497), correlated with younger PD onset with a 4.4-year decrease in mean age of onset (Hassan et al., 2016). These observations lead us to believe that in order to determine whether D3R density changes contribute to the development of PD, we need to take different genotypes of D3R into consideration.

In other words, there is no clear indication that D3R expression can be used as a diagnostic marker for early onset of PD. Although most studies mentioned above suggested the possibility, further studies are needed to clarify the role D3R plays in PD prediction. Further studies should clarify whether changes in D3R appear because of the pathological changes of PD or D3R changes induce PD pathogenesis. Furthermore, the degree to which one D3R mutation or various genotypes influence PD pathogenesis is of importance for further research. It should be noted, there is debate about evidence of changes in D3R being used as signs of preclinical or prodromal PD. However, we hope that in-depth research can help people find an early stage marker of PD as soon as possible.

4 Involvement of D3R in PD treatment

4.1 Change of D3R in PD development

Similar to the role of D3R in predicting PD occurrence, the changes of D3R in the SN and striatum during PD development are conflicting. Some studies have shown reduced D3R expression within the striatum in parkinsonism rats (Favier et al., 2017), monkeys (Morissette et al., 1998), and drug-naïve PD patients (Boileau et al., 2009). However, other studies indicated that D3R or mRNA expression was up-regulated in Parkinsonism rats (Sun et al., 2013b) and cats (Wade et al., 2001).

The controversies involving D3R expression in PD models and patients may be related to the time course of PD. One study indicated that D3R mRNA increased six-fold by 2 weeks and then decreased in baboons after MPTP administration (Todd et al., 1996). Medication may also alter the expression of D3R protein. Researchers believe that decreased expression of D3R may be reversed by long term L-DOPA treatment (Bezard et al., 2003), or other D1R agonist therapies (Morissette et al., 1998). Furthermore, although D3R may lead to the decrease of DA in the synaptic cleft due to its role as autoreceptor in the presynaptic membrane; it should be mentioned that the formation of D1R-D3R heteromers which appears mostly postsynaptically(Marcellino et al., 2008) leads to postsynaptic signaling similar to D1R activation. A function significantly different than D3R’s role as autoreceptor(Schmauss, 2000). D3R stimulation potentiated significant D1R mediated locomotor activation in reserpinized mice PD models (Marcellino et al., 2008), likely due to the fact that there is only weak coupling between the D3R promoter and Gi/o in D1R-D3R heteromer. Instead, D3R enhances D1R signaling over the Gs/olf complex, through allosteric receptor-receptor interactions (Fuxe et al., 2015). Therefore, this does not exclude the possibility that increased D3R could be a diagnostic criterion for early onset of PD as we mentioned earlier in this review.

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Despite inconsistencies that exist, we believe the activities of D3R are reduced in all these studies. Only D3R agonists are routinely used in preclinical and clinical interventions of PD; PD research studies seldom mention D3R antagonists.

4.2 D3R agonists in alleviating PD symptoms

Therefore, D3R agonists attract more and more attention in the treatment of PD in *in vivo* and *in vitro* models.

In animal studies, D3R agonists alleviated DA depletion in the striatum, attenuated DAergic neuron cell death in the SN, ameliorated microglial activation, and improved behavioral performance in Parkinsonism mice. These effects appear to be D3R dependent as they did not appear in D3R KO mice or in mice that received D3R antagonist pretreatment (Lao et al., 2013; Li et al., 2010a).

In clinical research trials, the efficacy of D3R preferential agonist, rotigotine, has been demonstrated in a series of phase III clinical studies with good tolerability and safety. Studies included patients with early and advanced stages of PD and established a dose-response relationship between escalating doses of rotigotine and improvements in PD symptoms (Benitez et al., 2014; Elmer et al., 2012; LeWitt et al., 2007; Pham and Nogid, 2008). Pramipexole, a D3R preferring agonist with a higher receptor selectivity, is effective as a monotherapy in early stage PD and able to delay the occurrence of dyskinesia in participants that fail to respond well to L-DOPA treatment(Antonini et al., 2010). Pramipexole can also be used as an adjunctive therapy in advanced PD (Antonini et al., 2010; Schapira et al., 2011) and should be established as a treatment option for all stages of PD patients (Frampton, 2014).

However, the principal for D3R agonists in PD treatment is still obscure, and we will discuss the potential mechanisms in detail in the following part.

5 Possible mechanism involving in D3R activation

5.1 D3R activation inhibits DA reuptake and breakdown in synaptic terminals

D3Rs are located both postsynaptically and presynaptically on DA target cells on DAergic neurons, respectively. Thus D3R works as an autoreceptor and generally provides an important negative feedback mechanism for neurotransmitter release that works in response to changes in extracellular neurotransmitter levels (Beaulieu and Gainetdinov, 2011). Therefore, it is believed that increased sensitivity or activation of D3R results in decreased DA content (Bustos et al., 2004). However, in certain circumstances, the activation of D3R might inhibit two main processes of DA metabolism including DA reuptake and breakdown, which may underlie the possible mechanisms by which D3R agonists alleviate PD symptoms.

a. D3R stimulation inhibits DA reuptake—The released DA in the synaptic space can be removed within milliseconds via DA reuptake through DAT. DAT pumps DA back into the cell to avoid persistent DA-induced biological effects. The transported DA can be

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encapsulated in vesicles for recycle by VMAT2. If effect of VMAT2 is hindered, there is a blockade of DA reuse and causes PD.

D3R activation reduces the affinity of DA for DAT and hinders DAT activity to induce persistence of DA biological effects. Castro-Hernandez et al found that a physical interaction between D3R and DAT reduced DA affinity for DAT in the absence of any changes in DAT density and subcellular distribution, and led to a decrease in DA uptake. This modulatory effect was D3R but not D2R dependent as the protective effect of pramipexole was absent in $D3R^{-/-}$ mice, but present in $D2R^{-/-}$ mice (Castro-Hernandez et al., 2015). Another demonstrated that D3R mediated long-term deficits in DAT function, and D3R inactivation attenuated methamphetamine-induced decreases in striatal DAT (Baladi et al., 2014). The direct modulation of DAT expression by D3R agonists was also examined. Pramipexole was able to reduced DAT immunoreactivity and lowered the Vmax for DA uptake into striatal synaptosomes in WT type mice, while this effect was not observed in D3R KO mice (Joyce et al., 2004). It is an interesting observation that the blocking of DAT may further activate D3R (Swant and Wagner, 2006), thus forming a positive feedback loop to block DAT.

D3R has also shown a close relationship with VMAT2. The D3R preferring agonist, quinpirole, can increase vesicular DA uptake in purified rat striatal vesicles; this effect was associated with redistribution of VMAT2 within nerve terminals (Truong et al., 2004). Pramipexole was also proved to be able to rapidly increase vesicular DA uptake in synaptic vesicles prepared from striatum of treated rats and this effect is associated with a redistribution of VMAT2 immunoreactivity within nerve terminals (Truong et al., 2003).

b. D3R stimulation inhibits DA breakdown—Although we cannot provide a direct example of interactions between D3R and DA metabolic enzymes, apomorphine, a D3R preferring agonist (D3R affinity 2~4 fold greater than for D2R) acts as a reversible competitive inhibitor of monoamine oxidase (MAO) A and B with IC_{50} values of 93 and 214 μM, respectively (Youdim et al., 1999).

While there is considerable evidence that D3R activation may regulate its transport and inhibit its metabolism (Figure 2), some studies do not support this conclusion. For example, some believe D3R antagonists promote the release of DA from mesolimbic DAergic neurons (Rivet et al., 1994), some believe that the protective effect of D3R agonists is independent of changes in DA concentration (Svensson et al., 1994). These views have some merits; in both PD patients and in animal models of PD, damage to the nigrostriatal pathway might result in a majority of the indicators below normal levels, making it easy to observe changes in protein expression and DA levels in these cases. Additionally, those changes in protein expression and dopamine level may be due to the overall therapeutic effect of D3R agonists.

These conflicting observations provide novel insights into the long-term antiparkinsonian actions of D3R agonists. From all these results, we believe that D3R agonists can be regarded as regulators of DA fluctuation, and might thus contribute to the treatment of PD.

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5.2 D3R activation decreases α-Syn accumulation

The protein α-Syn is detrimental to DAergic neurons in the SN, and may result in the formation of Lewy bodies and subsequent cell death. Many studies suggested that D3R agonists may exert neuroprotective effect through modulating abnormal aggregates of α-Syn (Figure 3).

a. D3R activation decreases α-Syn expression—D3R activation is believed to inhibit α-Syn expression in animal models and PD patients. Pramipexole was proved to be able to decrease α-Syn expression in a mouse PD model (Zhang et al., 2017) and in PD patients (Luo et al., 2016), measured by western blot or serum exosomes analysis.

b. D3R activation inhibits α-Syn aggregation—D3R activation also inhibits the aggregation of α-Syn. When co-incubated with an α-Syn solution, ropinirole inhibited α-Syn oligomer formation in an *in vitro* study (Ono et al., 2013). A study showed that α-Syn aggregate inclusions distributed both in mesencephalic DAergic neuron cell bodies and dendrites were dramatically reduced by quinpirole. This effect was significantly antagonized by the D2R/D3R antagonist sulpiride (Bono et al., 2018). A recent study published by the same group showed that nicotine could inhibit the accumulation of α-Syn though a D3R-nAChR heteromer. This effect was disrupted by D3R-nAChR heteromer specific interfering TAT-peptides (Bono et al., 2019). Another study proved that the co-incubation of D-520, a newly developed D3R selective agonist with K_i(D2R)/K_i(D3R)=119. inhibited α-Syn aggregation, reduced the toxicity of α-Syn when compared to control group (Modi et al., 2014). It is worth mentioning that some researchers believe that phosphorylated α-Syn accounts for 90% of α-Syn aggregates in Lewy bodies(Karampetsou et al., 2017), while pramipexole inhibited α-Syn phosphorylation to alleviate the formation of this neurotoxic aggregation (Chau et al., 2013).

c. D3R activation promotes α-Syn clearance through autophagy—The scavenging effect of D3R agonists on α-Syn may depend on autophagy (Figure 3). Autophagy helps remove abnormally aggregated proteins via lysosomal degradation, and its dysfunction is involved in the occurrence of PD.

One *in vitro* study demonstrated that co-incubation of rotenone treated PC12 cells with pramipexole led to a promoted clearance of α-Syn secondary to the up-regulation of Beclin1 (BECN1), an autophagy-associated protein. This effect was DR dependent because the R(+) enantiomer of pramipexole, which is devoid of agonist activity, showed no similar effect on autophagic markers or autophagosome formation (Wang et al., 2015a). And we believe that D3R may play an more important role than D2R as that D3R blockade seemed to be more effective than D2R blockade in suppressing the expression of autophagy related proteins, such as microtubule-associated protein 1 light chain 3(LC3)-II and BECN1 (Wang et al., 2015a). Similar results were also observed in an animal study which showed a massive aggregation of autophagosomes/autophagic vacuoles when using pramipexole (Li et al., 2010b).

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5.3 D3R activation enhances secretion of BDNF

Brain derived neurotrophic factor (BDNF) plays an important role in processing chemical communication, facilitating the survival and maturation of DAergic neurons and enhancing functional re-innervation in the adult brain striatum. Degeneration of DAergic neurons is found in the absence of BDNF while enhanced levels of BDNF may improve symptoms in PD patients (Jiang et al., 2019).

In an *in vitro* experiment, researchers found that pramipexole rescued TH+ and Microtubule-Associated Protein(MAP)+ neurons injury, and this protective effect was dependent on the release of BDNF (Imamura et al., 2008). Another study demonstrated that when primary mesencephalic cultures were co-incubated with conditioned medium from pramipexole or ropinirole treated primary cultures, the number of DAergic neurons was significantly increased. This protective effect could be blocked or diminished by BDNF neutralizing antibodies or by D3R antagonists, but not by D2R antagonists (Du et al., 2005). Other groups have reported similar findings. The protective effect of D3R activation disappeared when neurons were antagonized by selective D3R antagonists, or by immuno-neutralization of BDNF. Besides, the protective effect is D3R and BDNF dependent, but not D1R and D2R dependent (Collo et al., 2018; Presgraves et al., 2004).

Moreover, not only does D3R modulate expression of BNDF, but also BDNF influences the normal expression of D3R in neurons (Guillin et al., 2001). BDNF increases striatal level of D3R via tyrosine kinase receptor B (TrkB), thereby activate the relevant pathways (Jeanblanc et al., 2006). Saylor et al found that young $BDNF^{+/-}$ mice expressed lower levels of D3R mRNA than wild type mice, while a single microinjection of BDNF restored the expression of D3R. This suggests that both D3R and BDNF play a synergistic role in protecting striatal neurons (Saylor and McGinty, 2010).

5.4 D3R activation ameliorates neuroinflammation

Neuroinflammation is a double-edged sword. Inflammation plays an important defensive role in maintaining CNS homeostasis. However, uncontrolled neuroinflammation can disrupt blood-brain barrier (BBB) patency and may continuously trigger neuronal cell death. Obvious symptoms of enhanced neuroinflammation have been observed in post mortem brains of PD cases while non-steroidal anti-inflammatory drugs (NSAIDs) have been proposed to play a protective role in PD patients (Vivekanantham et al., 2015; Wahner et al., 2007).

It was observed that pramipexole treatment significantly alleviated microglial activation, attenuated DAergic neuron loss in SN and improved rotarod performance in an animal study (Li et al., 2010b). Other studies demonstrated that pramipexole could block the secretion of inflammatory factors, alleviate nerve inflammation and inhibit astrocytes activation (Kang et al., 2016; Lieberknecht et al., 2017).

The anti-inflammatory effect observed above is D3R dependent. A novel D3R preferring agonist D264 was shown to exert a protective effect in two mouse models of PD. Pretreatment with D264 seven days before MPTP or lactacystin administration dramatically improved behavioral performance, attenuated neuron loss through ameliorating microglial

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activation and increasing BDNF levels; these protective effects could be blocked by administering a D3R antagonist U99194 (Li et al., 2010a).

Contradictory evidence has also been presented. Although continuous pramipexole administration produced significant preservation of TH+ cells degeneration and alleviated TH+ terminals loss in parkinsonism rats who received stereotaxic injection of lipopolysaccharide (LPS) into SN, there was no effect on the expression of inflammatory markers; the authors believed that the protective effect of pramipexole could be due to enhanced tolerance to inflammation (Iravani et al., 2008).

We have proposed that D3R activation might enhance inflammation in the early stage of PD pathogenesis. So what leads to conflicting evidence? We think that is partly due to the complicated role of D3R in modulating inflammation. A study has shown that when Chinese hamster ovary cell (CHO) cells which overexpress D3R were activated by low concentration of DA, the release of arachidonic acid (AA) was inhibited, while high concentration of DA increased the release of AA. This suggested that excessive activation of D3R might be associated with inflammation, while moderate activation might play an anti-inflammatory role (Nilsson et al., 1999).

5.5 D3R activation alleviates oxidative stress injury

Oxidative stress is believed to be involved in PD. Increased lipid peroxidation and impaired mitochondrial function are found in the SN of PD patients. In numerous experimental models, exogenous toxins such as MPTP produce free radicals which induce PD (Zou et al., 2000). Rotigotine induced neuroprotective effect against glutamate toxicity in primary dopaminergic cultures through significantly decreasing the production of free radicals via dopamine receptor stimulation (presumably via the D3R) (Oster et al., 2014) . Thus, it is possible that D3R activation may influence PD progression through its antioxidant effect.

D3R activation was shown to inhibit reactive oxygen species (ARO) generation in neurons or animals. Pramipexole inhibited the production of mitochondrial ROS and prevented cell death, when compared with SH-SY5Y cells treating with H_2O_2 (Ferrari-Toninelli et al., 2010). Rotigotine significantly alleviated rotenone-induced primary mesencephalic neuronal death due to the significant attenuation of ROS production (Radad et al., 2014). An *in vivo* study showed that treating mice with MPTP increased lipid peroxidation products and loss of TH+ DA neurons in SN, while pramipexole treatment inhibited lipid peroxidation and protected SN injury (Zou et al., 2000).

The reason may be that D3R activation increases the level of enzymes which reduce ROS. Pramipexole was shown to normalize the level of Glutathione (GSH) and GSH peroxidase (Lieberknecht et al., 2017) in animal models of PD. Ropinirole is believed to increase the activities of GSH, catalase, and Superoxide dismutase which scavenge ROS, while pretreatment with D2R/D3R antagonist blockers abolished this protective effect (Iida et al., 1999).

Although most authors believed that D3R activation is necessary for the demonstrated reduction in ROS injury (Li et al., 2010a), some have shown that this can be independent of

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D3R activation (Le et al., 2000). Although more research is needed to clarify this issue, both the antioxidant and D3R activating engagements of D3R agonists play critical roles in its neuroprotective actions in PD treatment (Ling et al., 1999).

5.6 D3R activation promotes neurogenesis

PD demonstrates obvious impaired neurogenesis. A hallmark of PD is the loss of TH+ neurons in the SNpc and the reduction of DAergic projections to the striatum, therefore increasing neurogenesis helps alleviate the symptoms of PD (Salvi et al., 2016). Although it was once believed that adult neurogenesis occurs only in the hippocampal dentate gyms (DG) and subventricular zone (SVZ) regions, recent studies have shown that newly generated neurons may also occur in areas previously considered as non-neurogenic, e.g., the striatum (Salvi et al., 2016).

There is close relationship between D3R and neurogenesis. The expression of D3R in the CNS occurs in the very early stages of development, and mainly exists in the site of neurogenesis (Van Kampen and Robertson, 2005). It was observed that in hiPSC-derived DAergic neurons, treatment with D3R preferring agonists such as quinpirole and ropinirole promoted the reproduction of neuronal progenitor cells (Bono et al., 2018). In one study, the results showed that there was significantly increased proliferation of neurons in the DG and doublecortin (DCX)+ neuroblasts in the striatum of pramipexole treated mice (Salvi et al., 2016). Other studies showed that the maximal dendrite length, number of primary dendrites, number of DAergic neurons and [^{3}H]dopamine uptake of TH+ neurons were significantly enhanced when treated with quinpirole and D3R agonist 7-OH-DPAT, while the neurotrophic effects were all eliminated when D3R was blocked (Collo et al., 2008; Van Kampen and Eckman, 2006). Another study in lesioned zebra finches showed that 7-OH-DPAT led to significant reduction of lesion size and increased numbers of migrating neuroblasts and newborn cells in the striatal vocal nucleus area X, while the same effect was not seen in D3R antagonist U99194 treated cohorts (Lukacova et al., 2016).

The studies above suggested that the increased neuronal production effect was conducted via a direct effect on D3R. In addition, rat experiments showed that D3R activation could significantly increase neurogenesis in SVZ and SNpc (Van Kampen and Robertson, 2005), which are also the most vulnerable regions in PD. Pramipexole significantly promoted neurogenesis in the SVZ area of adult mice or rats, manifested by enhanced neuron number, neuronal differentiation, S-phase population at cell cycle and incorporation of BrdU, which could all be blocked by D3R antagonist U99194A. Pramipexole also increased the number of GFAP-positive cells and enhanced the expression of neuronal markers DCX and MAP2, and resulted in enhanced motor activity (Merlo et al., 2011; Winner et al., 2009).

5.7 D3R synergistically promote biological effect of D1R stimulation

Most DR agonists are for the D1R and D2R families, or the D2R family. The use of D1-selective/preferring agonists in PD therapeutics is an ongoing area of research. However, among all of these DRs, D1R is the most abundantly expressed receptor in the striatum (Perachon et al., 1999) and is believed to play a critical role in PD pathogenesis and treatment. Clinically, dopamine agonists with the highest D1R affinity have an efficacy most

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similar to L-DOPA, although not as effective. The full activation of D1R is the key to directly alleviate PD related symptoms (Lewis et al., 2006). Increased D1R expression is considered one of the critical elements for establishing a given dopamine agonists' clinical sensitivity to reduce PD symptoms (Hisahara and Shimohama, 2011). Deficiencies in D1R expression have led to Parkinsonian motor symptoms in animal studies (Centonze et al., 2003). It could be a logical conclusion that the synergistic effect between D3R and D1R may also participate in the alleviating effect of D3R agonists in PD.

The interaction between GPCRs may interfere with the GPCR signaling in both quantitative (ligand affinity) and qualitative (downstream pathway disruption) ways. It was proved that the interaction of D3R on D1R increases the affinity of D1R with its ligand, but has little effect on the affinity of D3R with its ligand (Marcellino et al., 2008). For example, selective D3R agonist PD128907 reduced the ED_{50} for the D1R agonist SKF 38393 from 56 to 4 nM in certain circumstances (Avalos-Fuentes et al., 2013). Once the affinity of DA to D1R is increased, G-protein signaling and cAMP accumulation is enhanced (Leggio et al., 2016). Deleting or pharmacologically blocking D3R attenuated important molecular markers in the D1R-neurons such as FBJ murine osteosarcoma viral oncogene homolog B(FosB), ERK, and histone-3 (H3)-activation (Solis et al., 2017), while activating D3R in the SN enhanced D1Rs to induce γ-aminobutyric acid (GABA) release in SN (Avalos-Fuentes et al., 2013) and striatum (Cruz-Trujillo et al., 2013). All these directly showed how D3R might enhance the physiological function of D1R neurons by activating D1R.

In one study, using risepinized mice in which DA was exhausted, locomotor activity was enhanced by the administration of D1R agonist. The effect of D1R agonist was potentiated through co-administration with the D3R agonist PD128907 dose-dependently. Furthermore, in light of the contested D3R selection properties of PD128907, D3R KO mice were also used. It was shown that although D1R agonist significantly enhanced the motor activation in both WT and D3R KO mice by itself, PD128907 significantly potentiated the locomotor activity induced by D1R stimulation in WT mice. However, similar results were not obtained with D3R KO mice (Marcellino et al., 2008). These results suggest that it is the activation of D3R which plays a critical synergistic role in promoting the D1R mediated behavioral effect.

5.8 Different voices

Although we have mentioned much evidence asserting the critical role that D3R may play in alleviating PD symptoms via differing mechanisms, studies have shown conclusions which are at odds with ours. Some studies conclude that D3R stimulation may be the source of debilitating PD symptoms. One study found that when S33084 - a selective D3R antagonist - was administered alone, Parkinsonian disability was alleviated in 6-OHDA injured rats (Mela et al., 2010) and a low dose of S33084 potentiated the anti-Parkinsonian effect of both L-DOPA and ropinirole (Silverdale et al., 2004). Nafadotride, another D3R antagonist, was reported to enhance locomotor activity at low doses in rats (Sautel et al., 1995). It was also reported that BP897, a D3R agonist, weakened the anti-Parkinson effect of L-DOPA (Hsu et al., 2004).

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When looked at on the whole, the conflicting nature of these reports lead us to believe that the role of D3R in the treatment of PD needs to be further discussed. We believe that in-depth discussion of these contradictions can help the research community better understand the role of D3R in PD. We can think of several reasons for the conflicting evidence present across the various studies. One, the therapeutic effects of D3R antagonists on PD may vary with the dosage. Although the mechanisms of D3R antagonists are still unknown. Some reports indicate that low doses of preferential D3R antagonist, S33138, was shown to potentiate the antiparkinson action of ropinirole. However, the benefits of this drug diminished at a high dose (Millan et al., 2008). Another D3R antagonist, nafadotride, similarly enhanced locomotor activity at a low dose, while this locomotor activation was not observed at a high dose or in some instance even decreased (Sautel et al., 1995). Still another study has shown that high doses of D3R antagonists produce an increase in disability, while low doses do not give such effects (Hadj Tahar et al., 1999). Two, the difference in D3R expression and binding state with its ligand should also be taken into consideration. Contrary results may be produced relative to differing states of stimulation or inhibition of D3R. Discrepancies may arise from changes relative to PD stage, treatment, or between species. For example, in one report that utilized MPTP-lesioned baboons, expression of D3R increased for two weeks to a peak of six fold before starting to decrease (Todd et al., 1996). The decline in caudate D3R expression after nigrostriatal degeneration was reversed after L-DOPA treatment (Quik et al., 2000). Changes were not limited to the expression of D3R but also the binding to exogenous ligands was shown to have been enhanced in the striatum of rats following repeated administration of L-DOPA (Bordet et al., 1997). Furthermore, the differences of D3R among species should also be taken into consideration. There is more widely distributed D3R in the striatum in humans and primates than in rats (Silverdale et al., 2004), a difference that may yield contradictory results when sorting out the effects of D3R agonists/antagonists. Three, the hypothesis that the inhibition of D3R alleviates PD symptoms has also been challenged due to the poor selectivity of some of the aforementioned D3R antagonists. Nafadotride, for example, is believed to be a D3R blocker but also binds with the 5-HT receptor (Audinot et al., 1998) and only shows 6.2 fold selectivity for D3R over D2R (Audinot et al., 1998). Another study used homozygous (D3−/−), heterozygous (D3+/−) mutant and wild-type (D3+/+) mice to analyze the effect of D3R agonists and antagonist in locomotor activity. Results of this study concluded that all D3R agonists decreased locomotion to a similar extent in all three genotypes while D3 receptor antagonist increased locomotor activity. However, there were no apparent difference between the D3−/−, D3+/−, and D3+/+ genotypes (Boulay et al., 1999). This research illustrates the possibility that there might be other alternative adaptive mechanisms involving still other receptors. Four, there is basis for reinterpreting some of the opposing results. In the instance where authors believe that D3R agonist weaken the anti-Parkinson effects of L-DOPA, it was concluded that D3R stimulation aggravated parkinsonian symptoms. However, it is reasonable to conclude that the partial D3R antagonist, BP897, could antagonize the anti-Parkinson effect of L-DOPA, whose metabolites are considered a complete agonist. After the dose of L-DOPA increased, the inhibitory effect of BP897 on the therapeutic effect of L-DOPA disappeared(Hsu et al., 2004), this supports our deduction and is a common phenomenon when discussing the effect of partial agonists. In addition, the above results also confirm that the dosage of L-DOPA may affect our judgment relative to the role of D3R

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in PD. Lastly, other authors believed that among various methods used to evaluate motor ability in different species of animals may lead to differences in the evaluation of the PD improvement effect in question (Hsu et al., 2004).

6 the role of D3R in PD associated non-motor symptoms

It is believed that D3R distributes abundantly in mesolimbic areas: nucleus accumbens, olfactory tubercle, amygdala, islands of Calleja, and in the striatum (Gurevich and Joyce, 1999; Jaber et al., 1996). Thus, activation or inhibition of D3R may be associated with the emotional, behavioral, motivational, and memory fluctuations which are commonly seen in PD patients. Common symptoms of these states include depression, anxiety, psychosis and cognitive defects.

6.1 Sensory and mood deficits

a. Depression—A reduction of the mesolimbic pathway precipitates the loss of motivation and anhedonia - symptoms of depression (Leggio et al., 2013). There is evidence that the down-regulation of expression and function of D3R at the mesencephalon exists in major depression (Leggio et al., 2013). The deficiency of D3R has also be posited to contribute to increased incidence of depressive symptoms (Moraga-Amaro et al., 2014), while D3R agonists are reported to exhibit antidepressant effects in a rat model(Rogoz et al., 2004).

Studies have reported that commonly used antidepressants could increase the expression, binding, or responsiveness of D3R in relevant brain areas such as the islands of Calleja and the nucleus accumbens - major projection areas of the mensolimbic dopaminergic system (Lammers et al., 2000; Maj et al., 1998). Therapeutic effects may depend on D3R as the preferential D3R agonist, cariprazine, exerted antidepressant effects in WT mice. However, this effect did not exist in D3R KO mice (Duric et al., 2017). Thus suggesting that activation of D3R be considered a potential method for the treatment of depression in PD rats model (Carnicella et al., 2014). Common clinically used D3R agonists, ropinirole and pramipexole, are reported to alleviate depressive symptoms in rats and PD patients further lending support to this hypothesis (Antonini et al., 2010; Mavrikaki et al., 2014).

b. Anxiety—D3R also plays an important role in anxiety. Results indicate that D3R KO mice show anxiety-like symptoms. Evidenced by thigmotaxis in openfield tests, a significant lower time spent in the lit compartment in the light-dark box test (Moraga-Amaro et al., 2014). 7-OH-DPAT and cariprazine, both are preferential D3R agonists, were found to exert anxiolytic-like effect in rats and mice models (Duric et al., 2017; Rogoz et al., 2004). Cariprazine was also believe to alleviate anxiety/depression vs placebo in clinical application (Marder et al., 2019). One clinically used anti-PD compound, ropinirole was proved to produce anxiolytic-like effects in the mouse, rat, and marmoset models (Rogers et al., 2000). Another *in vivo* study suggested that activation of D3R be considered a potential method of treatment for anxiety and depression in PD rat models when compared with D1R and D2R activation (Carnicella et al., 2014).

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c. psychosis—Psychosis is a common neuropsychiatric symptom of PD (Bleickardt et al., 2012). Treatment with dopaminergic medication can also induce psychosis. DR agonists are more likely to induce psychoses than L-DOPA(Bleickardt et al., 2012) - making DR agonist therapy a critical risk factor for PD psychosis (Han et al., 2018). The effect of dopamine agonists on psychosis may be closely related to prepulse inhibition (PPI). PPI is a neurological phenomenon defined by the reduction in startle magnitude following a weak prepulse (or prestimulus) and is used for the measurement of sensorimotor gating (Weber et al., 2009). PPI reduction (or deficit) is detected in schizophrenia patients and is among the most consistent and robust markers for this disorder (Swerdlow et al., 2006).

Many studies have shown that PPI is related to 5-HT and NMDA receptors, while D3R has been given more attention recently. Apomorphine (Yang et al., 2017), ropinirole(Giakoumaki et al., 2007), quinpirole (Nespor and Tizabi, 2008), and pramipexole (Chang et al., 2010) were all believed to induce a significant PPI reduction or deficit in animal models or human studies. It is thought that this effect of PPI reduction may be mediated by D3R agonism. Selective D3R antagonist, Y-QA31, was shown to reverse PPI perturbation in methamphetamine induce schizophrenia models (Sun et al., 2016). A D3R active drug, (S)-pramipexole, decreased PPI when infused into the NAc and islands of Calleja, in a dose-dependent manner. While (R)-pramipexole, a D3R-inactive molecule, had no effect. Moreover, the PPI disruptive effect of pramipexole were prevented by D3R-selective antagonist (Chang et al., 2012). Buspirone was also found to counteract the disruption of PPI induced by MK801 in WT mice, subsequently exerting an antipsychotic-like effect. This effect may be mainly driven by antagonist activity at D3Rs as the counteracting effect disappeared in $D3R^{-/-}$ mice (Torrisi et al., 2017).

These observations indicate that the PPI disruption seen with DR agonists may be mediated by D3R, however the role of other DRs cannot be ruled out(Varty and Higgins, 1998). Alternative explanations posit that D1R (Ralph-Williams et al., 2003) or D2R (Ralph et al., 1999) are essential for the disruption of PPI but not D3R (Ralph et al., 1999). This may be due to the various mechanisms in which DR agonists induce psychosis. For example, it was reported D2R antagonists inhibited apomorphine but not pramipexole induced PPI deficit, while D3R antagonists inhibited pramipexole but not apomorphine induced PPI deficit (Weber et al., 2008; Weber et al., 2009; Zhang et al., 2007). Furthermore, D3R Ser9Gly polymorphism may also influence their effect on PPI, demonstrated in one human study by the fact that Gly/Gly individuals had the lowest PPI while Ser/Ser individuals had the highest PPI (Roussos et al., 2008). Despite the controversies surrounding the mechanisms underlying psychosis-like symptoms, much consideration to this side effect is needed when using DR agonists. Best clinical practices, such as the reduction of doses or introducing antipsychotic medications if necessary, should be followed.

6.2 Dementia

The striatum is not only critically important in motor functions, but also plays important role in cognitive functions. D3R receptors are proved to specifically participate in cognitive aspects of striatal functions (Morissette et al., 1998).

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D3R expression was shown to be severely reduced in AD patients (Kumar and Patel, 2007). Having PD with an additional diagnosis of dementia correlated with lower D3 receptor density. Correspondingly, non-demented PD cases have elevated levels of D3R binding (Joyce et al., 2001).

When pramipexole was used to treat mild-moderate AD individuals, 13/16 patients showed improved cognition (Bennett et al., 2016). Another report in bipolar disorder also confirmed the therapeutic effect of pramipexole in cognitive impairment (Aprahamian et al., 2013). However, the reasons are still obscure.

Some rat experiments showed that D3R activation could significantly increase neurogenesis in SVZ and striatum (Van Kampen and Robertson, 2005), the vulnerable regions in PD. That may partially explain why treating with pramipexole could restore the synaptic transmission and Long-Term Potentiation (Castro-Hernandez et al., 2017).

However, there are also studies which do not support the view that D3R activation promotes cognitive function (Chang et al., 2018; Sun et al., 2013a). Whether activation of D3R may alleviate dementia in PD needs validation through large-scale clinical trials.

6.3 Impulse control disorders

ICDs (such as, but not limited to, gambling disorders, hypersexuality, and compulsive eating and shopping) have been reported in PD. ICD incidences are especially pronounced in PD patient populations who have received DA replacement therapies (Voon and Fox, 2007), and as such DR agonists are considered a major risk factor for ICD (Marvanova, 2016). ICDs were more frequent in patients taking agonists than a L-DOPA monotherapy (Fasano and Petrovic, 2010), while the D3-acting effect was statistically associated with ICD development (Fasano and Petrovic, 2010; Moore et al., 2014). Incidences of ICD are also associated with the use of L-DOPA, and the combination of L-DOPA and dopamine receptor agonists showed higher incidence of ICD than dopamine receptor agonists alone(Weintraub et al., 2010). The reason for these outcomes may lie in enhancement of D3R expression and binding activity as a result of chronic L-DOPA treatments (Cote and Kuzhikandathil, 2015), however there are many issue that still need to be elucidated further regarding this hypothesis. For one, D3R binding in ventral striatum has been shown to be lower in PD patients with ICD compared with those without, and also correlated with the severity of ICD (Payer et al., 2015).

Controversy between these studies also may be due to the differing genotypes of D3R. Researchers testing the association between ICD and D3R allelic variants, showed that D3R Ser9Gly (rs6280) genotype was significantly associated with ICD. In patients with this genotype, it is likely that increased D3R-ligand affinity, due to the gain-of-function conferred by the glycine residues, could impair reward-risk assessment and ultimately lead to ICD (Krishnamoorthy et al., 2016). However, another study discussed the association between the polymorphisms of 13 candidate genes and suggest that the independent contribution of a single D3R polymorphism in ICD is too low to be detected (Kraemmer et al., 2016). Some researchers believe that the selectivity for D3R over D2R should be taken into account and suggest that the incidence of ICD may be related to the affinity of D3R/

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D2R. This theory concludes that for a medicine - the higher the affinity of D3R/D2R, the higher the proportion of ICD induced by the medicine - for a given patient population (Seeman, 2015). Other possible reasons for variable incidences of ICD may also include: routes of administration (oral D3R agonists have higher risk of ICD development than transdermal(Garcia-Ruiz et al., 2014)), differing dosage (high D3R agonists dosage often means high frequency of ICD(Hassan et al., 2011)), or age of subjects (younger people may be better able to act on their impulses than seniors (Hassan et al., 2011)).

7 Role of D3R in treating L-DOPA induced dyskinesia

L-DOPA therapy remains the gold standard for PD treatment, however, long term L-DOPA exposure is closed related with many side effects, among which the commonest one is L-DOPA-induced dyskinesia (LID), or L-DOPA-induced abnormal involuntary movements (AIMs). The incidence of LID in PD patients receiving L-DOPA treatment for over 5 years is 50% (Dragasevic-Miskovic et al., 2019). Investigators are therefore committed to developing new PD drugs that will not cause LID, or drugs that can be combined with L-DOPA to reduce the onset of LID. D3R might be a target.

Some researchers believe that D3R expression is uppregulated in the LID patients receiving long-term treatment with L-DOPA (Aristieta et al., 2012; Bezard et al., 2003; Payer et al., 2016). Not only the expression of D3R, but also the binding of D3R was higher in LID monkeys or patients when compared to non-dyskinetic PD or normal counterparts (Guigoni et al., 2005; Payer et al., 2016), which hinted the role of D3R in LID. The overexpression of D3R induces behavioral sensitization in parkinsonian subjects, which subsequently leads to the occurrence of LID when treated with L-DOPA (Guillin et al., 2001). Down-regulating the expression of D3R in the striatum (Wang et al., 2015b), or blocking D3R (Cote et al., 2014), reversed motor fluctuations in rat PD models in which D3R expression was elevated.

D3R selective agonists can be used for the treatment of LID (Simms et al., 2016; Utsumi et al., 2013). However, what puzzled us is why D3R agonists hinder the occurrence of LID when D3R elevation or activation is believed to contribute to LID. Here is a brief explanation. Actually, it is D1R rather than the D3R activation contribute to LID. Long term L-DOPA administration may induced hypersensitivity of D1R, thus enhance GABA release and cAMP accumulation, which may play a role in LID occurrence (Rangel-Barajas et al., 2011). But D1R hypersensitivity can be modulated by D3R. L-DOPA-induced D3R overexpression principally occurs in D1R-containing neurons but shows relatively lower co-expression in the D2R-containing neurons (Solis et al., 2017). That may because D3R combines with D1R to form a heteromeric complex which plays an important part in LID (Fiorentini et al., 2008; Solis et al., 2017). There is a close relationship between the expression of D1R-D3R heterodimer and the occurrence of LID (Solis and Moratalla, 2018). An interaction between D3R and D1R could increase the binding affinity between D1R and DA, and enhance the density of D1R due to the lack of internalization of D1R (Fanni et al., 2018). In addition, the expression of D3R induced by long term L-DOPA treatment is instrumental in activating the downstream signal pathway of D1R, which aggravates the oversensitivity of D1R (Azkona et al., 2014).

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This proposed explanation leads to an interesting conclusion, that is, balancing and normalizing the activation of D3R may relieve the fluctuation of D1R sensitivity, thus avoiding the occurrence of LID; overactivation of D3R may induce LID, while blocking D3R activation may lead to PD symptoms. Some studies confirmed our deduction. When D3R full agonists, such as PD128907 (K_i was 0.4 nM (Scheideler et al., 1997)), were co-administered with D1R agonists (such as SKF38393) in rat experiments, there were severe exacerbation of LID (Lanza et al., 2018). When a partial agonist BP897 (K_i was 0.92 nM (Garcia-Ladona and Cox, 2003)) was administrated to animals in combination with L-DOPA, not only LID was attenuated, there was also no influence on the therapeutic effect of L-DOPA (Bezard et al., 2003). However, when a specific D3 receptor antagonist was co-administrated with L-DOPA, LID severity was alleviated but PD-like symptoms reappeared (Bezard et al., 2003). The suggestion that both D3R selective antagonists and partial agonists are pharmacotherapeutic candidates for the treatment of L-DOPA-associated AIMs in patients with PD (Mela et al., 2010; Riddle et al., 2011) can also be supported by our deduction.

Normalizing the activation of D3 receptor might attenuate LID without affecting the therapeutic effect produced by L-DOPA. Overactivation of D3R may induce LID because it enhances the density of D1R or augments D1R activity. Inhibiting D3R totally may cause damaged alleviation in PD symptoms due to the protective roles D3R played in PD therapy. The best approach is to mildly activate D3R (see Figure 4).

This view is in accordance with animal tests and clinical practice. SK609 (a D3R selective agonist, Ki=103 nM (Xu et al., 2017b)) notably improved the performance of the Parkinson like symptoms but did not induce AIMs and even reduced AIMs when co-administrated with L-DOPA (Simms et al., 2016). Pramipexole (K_i=10~12.6 nM (Millan et al., 2000; Millan et al., 2002)) was shown to be more effective than ergotamine D1R/D2R agonists in alleviating LID when co administrated with L-DOPA. It has been reported that when treated with a partial D3R agonist, the improvement in LID is associated with a worsening of Parkinsonism. In other words, the reduction in LID occurs at the expense of the anti-parkinsonian effects of L-DOPA (Hsu et al., 2004). This conclusion is in good agreement with our results.

Although we have shown many results that demonstrate the reliability of our conclusion, there are still some reports which give inconsistencies. Some results show no differences in striatal D3R expression between normal and PD patients (Hurley et al., 1996). Others studies - where chronic L-DOPA treatments produced AIMs - reported that co-treatment with D3R antagonist, S33084, and L-DOPA shows no alleviating effect either in terms of AIM frequency or amplitude in rats (Mela et al., 2010). Similar results were also obtained in MPTP treated marmosets (Silverdale et al., 2004). Other influencing factors for these results could be to blame. One, doses of D3R agonists/antagonists may exert influence on LID presentation. One Study has shown that high doses of D3R antagonists show a reduction of LID, while low doses do not show such an effect (Hadj Tahar et al., 1999). Two, doses of L-DOPA may influence the D3R antagonists' effect on LID. According to the receptor competition theory, increased dopamine induced by enhanced doses of L-DOPA can competitively inhibit the binding of antagonist to D3R. Therefore, the dosage of L-DOPA

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may affect the therapeutic benefits of D3R antagonist on LID. Three, there is evidence that the pathogenesis of PD may also change with respect to the progress of LID. There is a hypothesis that the development of LID reflects D3R insensitivity in an early age and sensitivity in the later age (Mela et al., 2010).Four, as mentioned previously, the discrepancy of D3R expression and binding state of its exogenous ligand between different PD stages, treatments, or species may also lead to deviations in experimental results. Lastly, we also acknowledge that in some studies, the activation of partial D3R agonists on other receptors may also help to relieve LID. For example, partial D3R agonist, BP897, was shown to attenuate LID and is also believed to be a potent ligand at 5-HT receptor (Heidbreder et al., 2005). Furthermore, activation of 5-HT also participates in alleviating LID (Bibbiani et al., 2001).

Therefore, we must mention that the hypothesis of the important role that D3R may play in the pathogenesis of LID is only a conjecture based on the review of the relevant literature, which we believe may too simplistic for discussing such a common and complicated side effect of L-DOPA. We cannot explain that why LID occurs after long term exposure to L-DOPA rather than immediately after several doses of L-DOPA or why a single dose of selective D3R antagonist shows no effect upon established LID. Others posit that the chronic aggravation induced via pathological damage, such as a loss of homeostatic synaptic plasticity in striatum or SN is also considered as a possible cause of LID (Borgkvist et al., 2018).

8 D3R changes for predicting prognosis of PD treatment

The change in D3R expression or function helps predict prognosis of PD treatment. For example, it was suggested that if D3R is elevated, response to DAergic drugs will be maintained. Correspondingly, loss of D3R density correlated with loss of response to DAergic drugs (Joyce et al., 2002). In an animal study, DR agonists showed better improvement in alleviating PD symptoms in animals with striatal over-expression of both D2R and D3R, when compared to those with over-expression of only D2R (Matsukawa et al., 2007).

However, most studies focus on D3R genotype in determining treatment plans. Changes in a single residue in D3R may cause fluctuation in agonist-dependent tolerance property (Gil-Mast et al., 2013), and affect the therapeutic effect of related drugs. In D3R, the most commonly researched polymorphic site is Ser9Gly. A study showed that D3R ser/Gly mutant is the main factor determining dose of DR agonists, and patients who carry Gly/Gly need higher doses of DR agonist to achieve identical treatment (Xu et al., 2017a).

Determining the precise D3R genotype may help identify potential side effects of PD therapy. A study has shown that the D3R Ser/Ser genotype is a predictor of gastrointestinal symptoms after L-DOPA treatment (Rieck et al., 2018). Other results showed that D3R Ser/Gly may lead to essential tremor in PD (Paus et al., 2010).

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9 Conclusions

For a long time, D1R and D2R have long been considered as critical participants in PD occurrence and progression. However, with in-depth understanding of the structure and function of D3R, people are paying more and more attention in the role of D3R in PD. But it is difficult to develop D3R-specific tracers and agonists as D2R and D3R show high similarity. We developed a quantitative autoradiography procedure for measuring the densities and mapping the regional distributions of D2R and D3R in the brain, and found that the striatal D3R is closely related with pathophysiological symptoms and prognosis results in PD patients. Therefore, we review the role of D3R in the pathogenesis, treatment and prognosis of PD, and try to provide insights for novel PD pharmaceutics via targeting D3R.

By summarizing literatures, we find that alterations of D3R involve in the early stage of PD and may be considered as an early stage biomarker for predicting PD occurrence. D3R agonists are also thought to be efficient in the treatment of PD, with their effect in increasing DA content, decreasing α-Syn accumulation, enhancing BDNF secretion, ameliorating oxidative stress and neuroinflammation, promoting neurogenesis and interacting with other DRs. Besides, Targeting D3R also helps in relieving some PD associated non motor symptoms and side effects of L-DOPA. Furthermore, D3R is also considered as an indicator for predicting prognosis of PD treatment. All of these suggested that D3R may be of great importance in the diagnosis, treatment and prognosis of PD. However, many questions need further clarification.

1. Whether the development of highly selective tracers or drugs for D3R will yield better diagnostic or therapeutic effects without unwanted side effects. We should avoid similar phenomena as valdecoxib, a highly selective inhibitor of COX2 with strong anti-inflammatory effects, which was unfortunately withdraw from the market due to severe cardiovascular side effects (Atukorala and Hunter, 2013).
2. Should the interactions between D3R and other GPCRs or other related proteins be taken into account in the diagnosis and treatment of PD? Our literature review indicates that interactions between D3R and other GPCRs or other related proteins (such as VMAT2) may be an important factor in the occurrence and development of PD, rather than D3R itself.
3. As mentioned earlier, D3R activation not only participates in the treatment of PD, but also help in alleviating the occurrence of LID. Both effects are achieved partly by regulating D1R activity. The critical questions are what’s the ideal affinity and selectivity of D3R agonists and what’s the optimized individual dosage in clinical practice?

Although much scientific research is needed to further reveal the roles of D3R in PD, we believe that the development of D3R specific tracers and drugs is important for the diagnosis and treatment of PD. While we do not expect D3R-related drugs will solve all the problems, each step of understanding D3R will bring us closer to an improved cure for PD.

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Highlights

- A novel procedure for quantitatively calculating the densities of D2R and D3R is recommended.
- The role of D3R in the pathogenesis, treatment and prognosis of PD is systematically summarized.
- Possible role of D3R in alleviating L-DOPA-induced dyskinesia and possible D3R agonists are introduced.
- The potential mechanisms of D3R activation in treating PD are extensively expounded.

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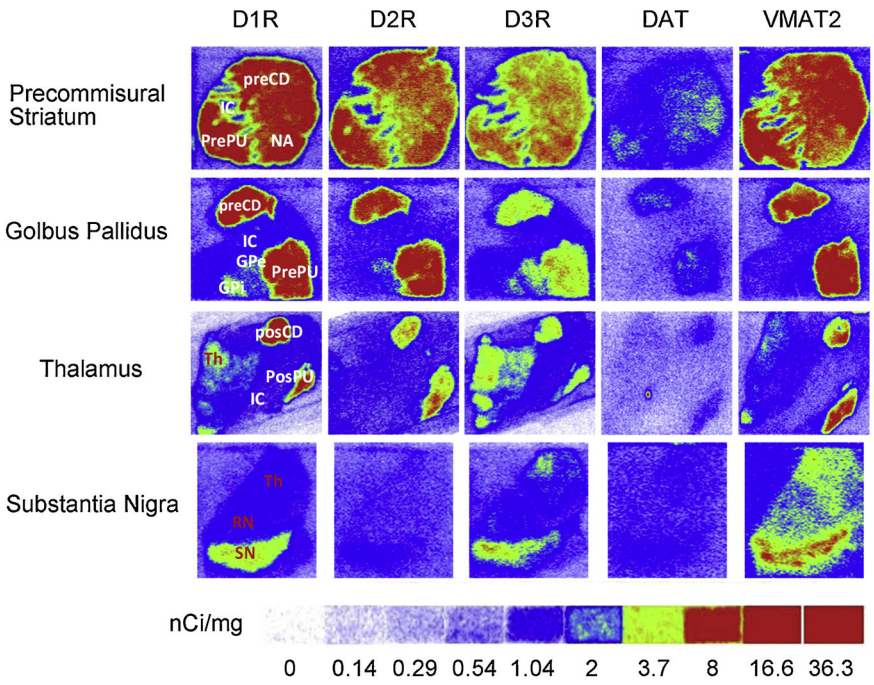

Fig 1. Autoradiograms show the differential distribution of D1R, D2R, D3R, DAT and VMAT2 in the striatal and extrastriatal regions of human brain sections.

[^{3}H]Microscale standards (ranging from 0 to 36.3 nCi/mg) were also counted for the calibration of radioactivity). The following CNS anatomical regions have been denoted: Precommissural putamen (**PrePu**); Precommissural caudate (**PreCd**); Nucleus accumbens (**NAc**); Internal capsule (**IC**). Globus pallidus external part (**GPe**); Globus pallidus internal part (**GPi**); Postcommissural putamen (**PostPu**); Postcommissural caudate (**PosCd**); Thalamus (**Th**); Substantia nigra (**SN**); Red nucleus (**RN**). ***D3R density is higher than D2R in Th, RN, SN and GPi.*** dopamine active transporter (**DAT**); vesicular monoamine transporter 2 (**VMAT2**).

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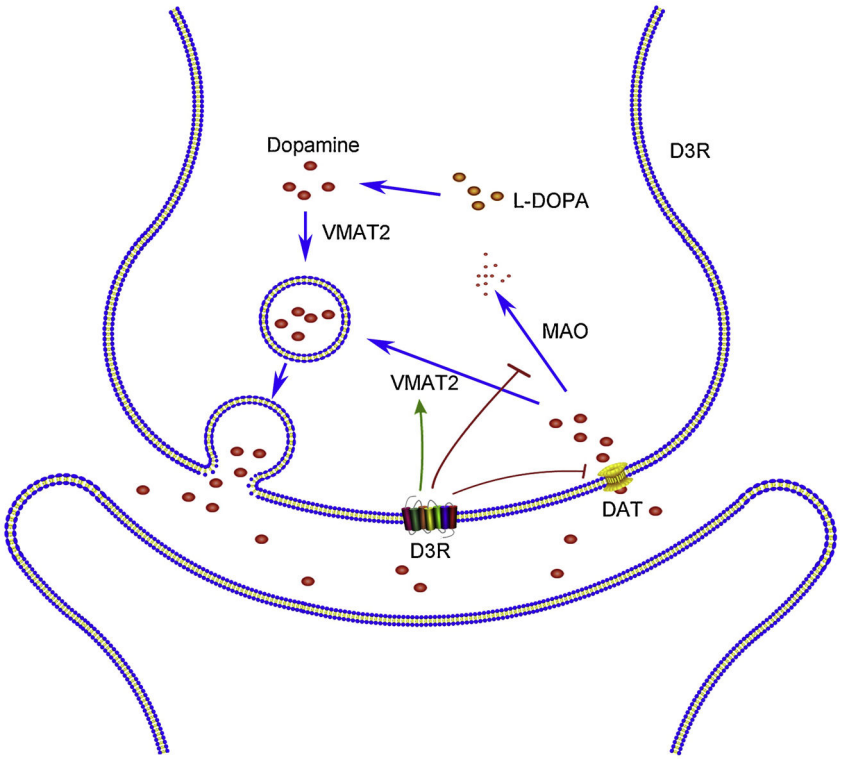

Fig 2. Effects of presynaptic D3R activation in modulating D3R content.

D3R promotes the function of VMAT2 to boost the release of DA, hinders DAT to restrain the reuptake of DA, and inhibits MAO to reduce the breakdown of DA, eventually augments the content of DA in the synaptic cleft. dopamine active transporter (**DAT**); vesicular monoamine transporter 2 (**VMAT2**); monoamine oxidase (**MAO**).

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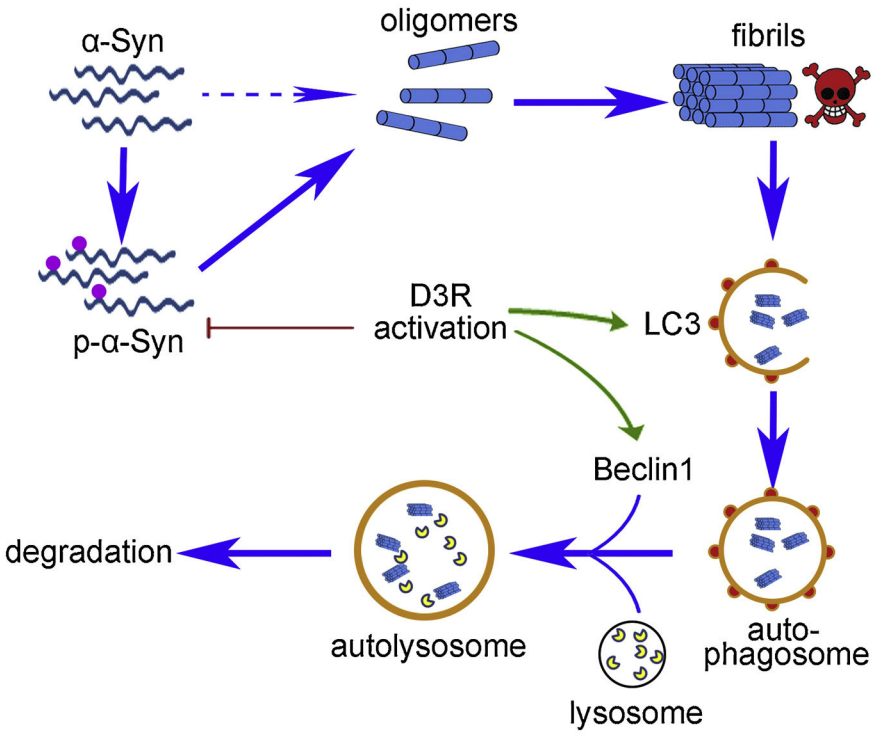

Fig 3. D3R activation inhibits abnormal aggregation and enhances clearance of α-Syn.

D3R activation hinders the phosphorylation of α-Syn to inhibit the abnormal formation of fibrils. Besides, D3R activation also enhances autophagy-dependent degradation of toxic fibrils by modulating autophagy related protein LC3 and Beclin1. α-Synuclein (**α-Syn**); microtubule-associated protein 1 light chain 3 (**LC3**).

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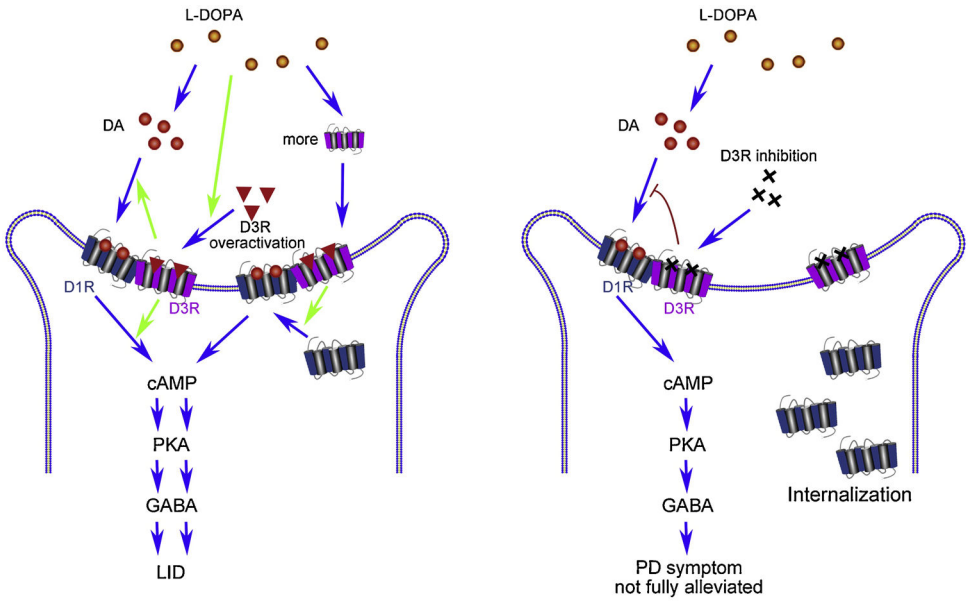

Fig 4. The relationship between D3R with LID.

Left penal: D3R exacerbates D1R hypersensitivity and leads to LID. D3R enhances the expression of D1R in the surface of neurons, increases the affinity of DA to D1R, and activates the downstream signal pathway of D1R, finally induces the oversensitivity of D1R, which leads to LID. Right panel: D3R inhibition relieves LID, but shows no effect on alleviating PD symptoms. D3R inhibition lead to the lack of D1R in the surface of neurons and the decreased affinity of DA on D1R, which induces damaged alleviation of DA agonists in PD symptoms. Dopamine (**DA**); cyclic adenosine monophosphate (**cAMP**); protein kinase A (**PKA**); γ -aminobutyric acid (**GABA**); L-DOPA induced dyskinesias (**LID**).

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Table 1

Structural, distributional and pharmacological properties of DR subtypes

	D1Rs		D2Rs		
Subtype	**D1R**	**D5R**	**D2R**	**D3R**	**D4R**
Number of amino acids	452 (Wang et al., 2014)	477 (Grandy et al., 1991)	443 (Dal Toso et al., 1989)	400 (Beaulieu and Gainetdinov, 2011)	387 (Beaulieu and Gainetdinov, 2011)
Molecular weight	50.5kD (Wang et al., 2014)	52.9kD (Grandy et al., 1991)	50.6kD (Dal Toso et al., 1989)	44.2kD (Beaulieu and Gainetdinov, 2011)	41.5kD (Beaulieu and Gainetdinov, 2011)
Sequence homology	---	49% with D1R (Grandy et al., 1991)	---	79% with D2R (Boeckler and Gmeiner, 2007)	53% with D2R (Missale et al., 1998)
Brain distribution	CPu, NAc, SN,OB, AM, FrC, Hip, CB (Beaulieu and Gainetdinov, 2011; Mishra et al., 2018)	PFC, PMC, Cg, Ent, SN,Hypo, Hip, DG, NAc, OTB (Beaulieu and Gainetdinov, 2011)	SN, VTA, Str , Hypo, Sept, AM, Hip (Beaulieu and Gainetdinov, 2011; Mishra et al., 2018)	NAc, OTB, IC, Str, SNpc, VTA, Hip, Sept (Beaulieu and Gainetdinov, 2011)	FrC, AM, Hip, Hypo, GP, SNr, Thal (Beaulieu and Gainetdinov, 2011)
Synapse location	Mainly Post (Beaulieu and Gainetdinov, 2011) and seldom Pre in PFC in primates (Muly et al., 2010)	Mainly Post (Beaulieu and Gainetdinov, 2011) and seldom Pre in PFC in primates (Muly et al., 2009)	D2s in Pre, D21 in Post (Cooper and Stanford, 2001; Rondou et al., 2010)	Pre & Post (Diaz et al., 2000; Stanwood et al., 2000)	Mainly Post (Rondou et al., 2010)
Affinity to DA (K_i value in nM)	~2500 (Sunahara et al., 1991)	~225 (Sunahara et al., 1991)	~500 (Rondou et al., 2010)	~2 (Sanchez-Soto et al., 2016; Scheideler et al., 1997)	~180-400 (Rondou et al., 2010)
Specific agonist	A-77636 (Kebabian et al., 1992) SCH23390 (Monti and Jantos, 2018)	Lack of	N-0437 (Van der Weide et al., 1988)	PD128907 (Millan et al., 2000; Scheideler et al., 1997) PF-529379 (Collins et al., 2012)	77-LH-28-1 (Del Bello et al., 2018) PD168077 (Sampson et al., 2014)
Related diseases	PD (Beaulieu and Gainetdinov, 2011), HD (Augood et al., 1997; Bibb et al., 2000),	ADHD (Gizer et al., 2009), MS (Giorelli et al., 2005)	SCZ (Seeman et al., 2005), Depr (Willner, 1997), PD (Kalia and Kalia, 2015; Prieto et al., 2011), SA (Le Foll et al., 2009), RSL (Keck et al., 2015)	PD, RLS (Cortes et al., 2016), SCZ (Gross et al., 2013), SA (Le Foll et al., 2014a), HD (Ariano et al., 2002), AD (Nakajima et al., 2013), Depr (Cao et al., 2010)	SCZ (Rondou et al., 2010), ADHD (Coghill and Banaschewski, 2009)

Caudate-Putamen (CPu), Prefrontal Cortex (PFC), Nucleus Accumbens (NAc), Olfactory Bulb (OB), Amygdala (AM), Frontal Cortex (FrC), Hippocampus (Hip), Cerebellum (CB), Prefrontal Cortex (PFC), Premotor Cortex (PMC), Cingulated Cortex (Cg), Entorhinal Cortex (Ent), Hypothalamus (Hypo), Dentate Gyrus (DG), Striatum (Str), Olfactory Tubercle (OTB), Ventral Tegmental Area (VTA), Septum (Sept), Islands of Calleja (IC), Globus Pallidus (GP), Substantia Nigra pars reticulate (SNr), Thalamus (Thal), Pre-synaptic location (Pre), Post-synaptic location (Post), Restless Legs Syndrome (RLS), Schizophrenia(SCZ), Substance Addiction (SA), Depression (Depr), Attention Deficit Hyperactivity Disorder(ADHD)