



Striatal $G\alpha_{olf}$ /cAMP Signal-Dependent Mechanism to Generate Levodopa-Induced Dyskinesia in Parkinson's Disease

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The motor symptoms of Parkinson's disease (PD) result from striatal dopamine (DA) deficiency due to a progressive degeneration of nigral dopaminergic cells. Although DA replacement therapy is the mainstay to treat parkinsonian symptoms, a long-term daily administration of levodopa often develops levodopa-induced dyskinesia (LID). LID is closely linked to the dysregulation of cyclic adenosine monophosphate (cAMP) signaling cascades in the medium spiny neurons (MSNs), the principal neurons of the striatum, which are roughly halved with striatonigral MSNs by striatopallidal MSNs. The olfactory type G-protein α subunit ($G\alpha_{olf}$) represents an important regulator of the cAMP signal activities in the striatum, where it positively couples with D_1 -type dopamine receptor (D_1R) and adenosine A_{2A} receptor ($A_{2A}R$) to increase cAMP production in the MSNs. Notably, D_1R s are primarily expressed in striatonigral MSNs, whereas D_2R s and $A_{2A}R$ s are expressed in striatopallidal MSNs. Based on the evidence obtained from parkinsonian mice, we hypothesized that in the DA-denervated striatum with D_1R hypersensitivity, a *repeated* and *pulsatile* exposure to levodopa might cause a usage-induced degradation of $G\alpha_{olf}$ proteins in striatal MSNs, resulting in increased and decreased levels of $G\alpha_{olf}$ protein in the striatonigral and striatopallidal MSNs, respectively. As a principal cause for generating LID, this might lead to an increased responsiveness to levodopa exposure in both striatonigral and striatopallidal MSNs. Our hypothesis reinforces the long-standing concept that LID might result from the reduced activity of the striatopallidal pathway and has important clinical implications.

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INTRODUCTION

By transducing extracellular signals carried by neuromodulators, the cyclic adenosine monophosphate (cAMP) signaling plays a crucial role in the regulation of neuronal activities in the brain. Multiple guanine nucleotide-binding protein (G-protein)-coupled receptor (GPCR) cascades regulate the intracellular levels of cAMP, which activates its key effector protein kinase A. Seven-transmembrane domain receptors can transmit extracellular signals to the intracellular signaling cascades through the activation of heterotrimeric G-proteins, which are composed of the guanine nucleotide-binding $G\alpha$ subunit and the dimeric $\beta\gamma$ subunits (Pierce et al., 2002). $G\alpha_s$ is the

predominant stimulatory G-protein subunit in the brain. However, in the striatum, $G\alpha_s$ is replaced by the olfactory type G protein α subunit ($G\alpha_{olf}$), which is encoded by the *GNAL* gene (Jones and Reed, 1989). Cellular $G\alpha_{olf}$ /cAMP signaling pathway represents a principal regulator for the striatal functions in normal physiological processes and pathological conditions (Hervé, 2011). It is worth noting that mutations in the *GNAL* gene have been identified as a cause for generating dystonia (Fuchs et al., 2013; Pelosi et al., 2017), suggesting that the $G\alpha_{olf}$ function might participate in the brain circuit involving motor control.

The motor symptoms of Parkinson's disease (PD) are caused by striatal dopamine (DA) deficiency, predominantly in the putamen, resulting from a progressive degeneration of nigrostriatal DA-producing cells (Kish et al., 1988; Goto et al., 1989). Although the DA replacement therapy remains the mainstay to treat PD symptoms, long-term exposure to dopaminergic drugs, particularly to the DA precursor levodopa, eventually causes adverse effects such as motor fluctuations and levodopa-induced dyskinesia (LID; Jenner, 2008; Calabresi et al., 2010; Bastide et al., 2015). LID is a major cause of disability in patients with PD, and occurs in approximately 80% of patients after 5 years of treatment with a daily administration of levodopa (Obeso et al., 1989; Luquin et al., 1992; Rascol et al., 2000). Importantly, once LID has been primed (or established), its severity progressively increases despite even when the used dosage of dopaminergic drugs is not increased (Brotchie, 2005). LID is known to be closely linked to the altered function of the DA signaling pathways in the striatum (Brotchie, 2005; Jenner, 2008; Bastide et al., 2015; Calabresi et al., 2016). It has also been suggested that LID is associated with the hypersensitivity of striatal MSNs to DA receptor stimulation and with ongoing deregulation of corticostriatal inputs, which activate striatal glutamate receptors, such as *N*-methyl-D-aspartate (NMDA) receptors (Brotchie, 2005; Jenner, 2008; Bastide et al., 2015; Calabresi et al., 2016). In this hypothesis article, we primarily considered the levodopa-induced changes in cellular $G\alpha_{olf}$ protein levels in the DA-denervated striatum as the key mechanism to increase the striatal responsiveness to DA receptor stimulation in LID.

$G\alpha_{olf}$ REGULATES THE AGONIST-INDUCED cAMP PRODUCTION IN STRIATAL CELLS

As being innervated by massive dopaminergic afferents originating from the midbrain, the striatum is highly enriched in DA receptors, which belong to a superfamily of GPCRs and are classified into two subtypes, D_1 - and D_2 -type receptors. Through their specific targeting of G proteins, the D_1 -type receptors (D_1 Rs) elicit the adenylyl cyclase type (AC) to increase the cAMP production, whereas the D_2 -type dopamine receptors (D_2 Rs) inhibit the cAMP production (Kebabian and Calne, 1979; Missale et al., 1998). Medium spiny neurons (MSNs) constitute more than 90% of the neuronal types in the striatum (Graybiel, 2008; Kreitzer, 2009; Gerfen and Surmeier, 2011). Anatomically, they are roughly halved with the MSN group to form the “direct” striatonigral pathway by the MSN group

to from the “indirect” striatopallidal pathway (Crittenden and Graybiel, 2011; Gerfen and Surmeier, 2011; Calabresi et al., 2014). The striatonigral and striatopallidal MSNs express D_1 Rs and D_2 Rs, respectively. Moreover, the striatopallidal MSNs, but not the striatonigral MSNs, are enriched in adenosine A_{2A} receptors (A_{2A} Rs), which are prototypical Gs-coupled receptors that elicit AC to increase cAMP production (Svenningsson et al., 1999; Schwarzschild et al., 2006; Fuxe et al., 2007). **Figure 1** depicts the cell-type specific localization of $G\alpha_{olf}$, D_1 R and A_{2A} R among the striatal MSNs that constitute the basic circuits of the basal ganglia.

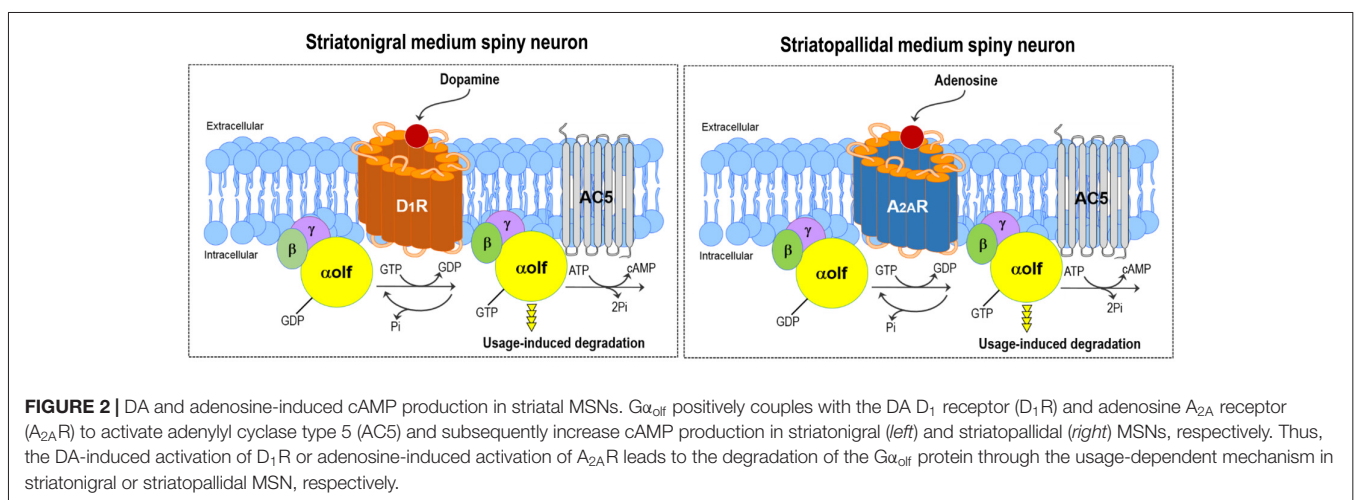
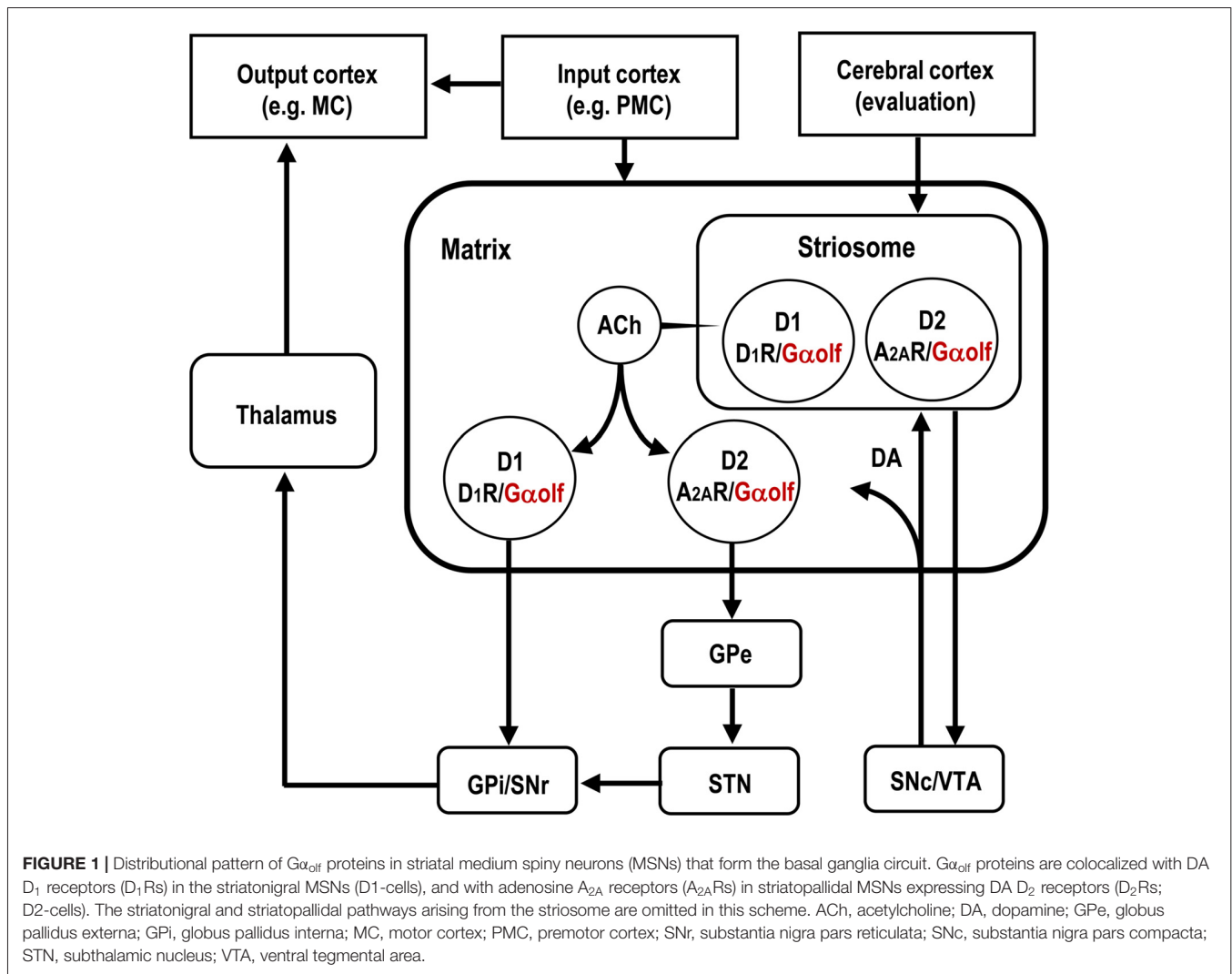
$G\alpha_{olf}$ is highly expressed in all striatal MSNs including those expressing the D_1 Rs and A_{2A} Rs (Kull et al., 2000; Hervé, 2011; Morigaki et al., 2017; see **Figure 2**). As $G\alpha_{olf}$ positively couples with D_1 R and A_{2A} R to activate the AC type 5 (AC5) and, thereby, increase the intracellular cAMP levels, it serves as the rate-limiting factor for both the D_1 R- and A_{2A} R-dependent cAMP production in striatal MSNs (Kull et al., 2000; Corvol et al., 2001). The $G\alpha_{olf}$ protein level plays a key role in regulating the D_1 R/cAMP- and A_{2A} R/cAMP-signal activities of striatonigral and striatopallidal MSNs, respectively. The D_1 R/ $G\alpha_{olf}$ -mediated increases in the cAMP levels cause the activation of the striatonigral MSNs (Hervé, 2011). On one hand, as D_2 R activation inhibits AC5 through $G_{i/o}$ proteins but A_{2A} R activation elicits AC5 through $G_{s/olf}$ proteins (Kull et al., 2000), the A_{2A} R/ $G\alpha_{olf}$ -signal stimulation functionally opposes the actions of D_2 Rs on the striatopallidal MSNs (Schwarzschild et al., 2006; Fuxe et al., 2007).

SUBDIVISIONAL AND COMPARTMENTAL LOCALIZATION OF $G\alpha_{olf}$ IN THE STRIATUM

Quantitative immunohistochemistry (IHC) has shown that the $G\alpha_{olf}$ protein is unevenly distributed within the mouse striatum, where it is highly concentrated in the dorsolateral striatum (Morigaki et al., 2017). Since the dorsolateral portion of the mouse striatum corresponds to the motor territory in rodents and is analogous to the putamen in primates (Graybiel, 2008), this strategic expression of $G\alpha_{olf}$ protein indicates that $G\alpha_{olf}$ may function as the stimulatory G protein that has a tight link to the basal ganglia “motor” circuit (Alexander and Crutcher, 1990) at the striatal level. With respect to the striatal compartments, there was a differential localization of $G\alpha_{olf}$ with higher densities of $G\alpha_{olf}$ proteins in the striosomes relative to the matrix compartment (Sako et al., 2010; Ruiz-DeDiego et al., 2015; Morigaki et al., 2017). This suggests that $G\alpha_{olf}$ may be a key molecule that determines differential responses between the striosome and matrix compartments to the D_1 R or A_{2A} R activation in the striatum at maturity.

HOMEOSTATIC REGULATION OF THE CELLULAR $G\alpha_{olf}$ PROTEIN LEVELS IN THE STRIATUM

Rodent animal models for PD (Iderberg et al., 2012; Francardo and Cenci, 2014) have so far been used to elucidate the regulatory mechanism for the striatal expression of $G\alpha_{olf}$. In



line with the evidence that there is a significant increase in $G\alpha_{olf}$ protein levels in the putamen of patients with PD

(Corvol et al., 2004), a dramatic increase in $G\alpha_{olf}$ protein levels has been identified in the DA-depleted striatum of rats

(Hervé et al., 1993; Marcotte et al., 1994; Penit-Soria et al., 1997; Corvol et al., 2004; Rangel-Barajas et al., 2011) and mice (Alcacer et al., 2012; Ruiz-DeDiego et al., 2015; Morigaki et al., 2017) with nigrostriatal 6-hydroxydopamine lesions. However, this upregulation of the $G\alpha_{olf}$ protein levels is not associated with a parallel increase of the $G\alpha_{olf}$ mRNA expression. Accordingly, the homeostatic regulation of $G\alpha_{olf}$ protein levels is thought to occur through post-translational mechanisms in the striatum, where the altered expression of the $G\alpha_{olf}$ protein depends directly on its usage rate (Hervé, 2011). The persistent lack in the use of D_1R and $G\alpha_{olf}$ could lower the $G\alpha_{olf}$ degradation rate and thereby result in the accumulation of $G\alpha_{olf}$ protein in the DA-denervated striatum of PD models. In agreement with this hypothesis, a total lack of D_1Rs by D_1R gene targeting induces a significant increase of the $G\alpha_{olf}$ protein levels without any changed expression of $G\alpha_{olf}$ mRNAs in the striatum of mutant mice (Hervé et al., 2001). In contrast, the decreased levels of striatal $G\alpha_{olf}$ proteins were found in mutant mice lacking the DA transporter (Hervé et al., 2001), which exhibit a marked increase in the extracellular DA levels leading to persistent activation of D_1Rs in the striatum (Giros et al., 1996). Importantly, the lack of $A_{2A}Rs$ in homozygous $A_{2A}R$ knock-out mice (Ledent et al., 1997) also results in an upregulation of $G\alpha_{olf}$ proteins with no obvious changes in the levels of $G\alpha_{olf}$ transcripts (Hervé et al., 2001). Collectively, the agonist-induced activation of D_1Rs (Hervé et al., 2001; Corvol et al., 2004, 2007; Alcacer et al., 2012; Ruiz-DeDiego et al., 2015) or $A_{2A}Rs$ (Hervé et al., 2001) might lead to the degradation of $G\alpha_{olf}$ proteins in striatal MSNs through posttranslational usage-dependent mechanism (see Figure 2).

$G\alpha_{olf}$ PROTEIN LEVELS IN STRIATONIGRAL AND STRIATOPALLIDAL MSNs IN LID

On the hypothesis that the upregulation of the $G\alpha_{olf}$ protein levels results from the disuse of the D_1Rs in the DA-depleted striatum in rodent models for PD, several studies with IHC and western blot analyses revealed that the $G\alpha_{olf}$ could be returned to normal levels by DA replacement with a daily exposure to levodopa in rodent models for PD with LID (Corvol et al., 2004; Rangel-Barajas et al., 2011; Ruiz-DeDiego et al., 2015; Morigaki et al., 2017). With respect to the striosome-matrix system, IHC studies revealed that the $G\alpha_{olf}$ levels were normally found in both the striosome and matrix compartments in PD with LID, although they were markedly increased in the matrix compartment, but not or only mildly increased in the striosome compartment, in PD (Ruiz-DeDiego et al., 2015; Morigaki et al., 2017). This novel finding indicates that there is a difference in the dopaminergic regulation of the $G\alpha_{olf}$ expression between the striosome and matrix compartments.

In situ proximity ligation assay (PLA) for dual-antigen recognition disclosed cell-type specific changes in the $G\alpha_{olf}$ levels in the DA-depleted striatum of mice with and without LID (Morigaki et al., 2017). The *in situ* PLA technique can indicate the presence of the $G\alpha_{olf}$ protein in close proximity

to the D_1R protein (D_1R - $G\alpha_{olf}$) or $A_{2A}R$ protein ($A_{2A}R$ - $G\alpha_{olf}$). Quantitative *in situ* PLA showed that DA depletion caused a marked ($\sim 90\%$) increase in the striatal levels of D_1R - $G\alpha_{olf}$ PLA signals, which were downregulated by a daily administration of levodopa. However, there remained a significant ($\sim 50\%$) increase in the striatal D_1R - $G\alpha_{olf}$ PLA signals in mice with LID when compared with normal controls. On one hand, quantitative *in situ* PLA also disclosed that a daily exposure to levodopa, but not DA depletion *per se*, caused a significant ($\sim 40\%$) decrease in the striatal $A_{2A}R$ - $G\alpha_{olf}$ PLA signals in the DA-depleted striatum of mice with LID. These findings indicate that, in the DA-depleted striatum, DA replacement could induce the downregulation of the $G\alpha_{olf}$ protein levels not only in the striatonigral MSNs but also in the striatopallidal MSNs.

An intriguing question is how the $G\alpha_{olf}$ protein levels are decreased in the striatopallidal MSNs in LID. In animal models with nigrostriatal 6-OHDA-lesions, persistent (chronic) DA depletion *per se* has been shown to cause no apparent changes (Ballarin et al., 1987; Herrera-Marschitz et al., 1994; Nomoto et al., 2000) or mild decrease (Pinna et al., 2002) in the extracellular levels of adenosine in the DA-denervated striatum. However, evidence shows that the striatal adenosine levels are elevated by the activation of NMDA receptors (Delaney and Geiger, 1998; Delaney et al., 1998), which can be enhanced by D_1R activation (Cepeda and Levine, 2012; Morigaki and Goto, 2015; see Figure 3). Interestingly, a *pulsatile* exposure to the D_1R agonist reportedly facilitated the NMDA receptor-evoked increase in the extracellular adenosine release in the rat striatum (Harvey and Lacey, 1997). This evidence suggests that, in the DA-depleted striatum with D_1R hypersensitivity, a repeated administration of levodopa may exert a *pulsatile* activation of D_1Rs , which subsequently facilitates the NMDA receptor-evoked increase in the extracellular adenosine levels. Moreover, in the DA-depleted striatum, the activation of NMDA receptor could lead to a marked increase in the extracellular adenosine levels and, then, indirectly activate $A_{2A}Rs$ (Nash and Brotchie, 2000). Thus, it is likely that the downregulation of the $G\alpha_{olf}$ levels in striatopallidal MSNs in LID might result from an increased usage of $G\alpha_{olf}$ proteins through the $A_{2A}R$ activation subsequent to the daily *pulsatile* activation of striatal D_1Rs . This notion also suggests that the striatal D_1R signals might play a critical role in the regulation of the $G\alpha_{olf}$ protein levels not only in the striatonigral MSNs, but also in the striatopallidal MSNs in the DA-denervated striatum. This consideration may corroborate the general concept that increased activities of striatal D_1Rs are requisite for the genesis of LID (Westin et al., 2007; Darmopil et al., 2009; Alcacer et al., 2012).

STRIATAL $G\alpha_{olf}$ /cAMP SIGNAL-DEPENDENT MECHANISM FOR GENERATING LID

Figure 4 shows the hypothetical representation of the $G\alpha_{olf}$ protein levels in striatonigral and striatopallidal MSNs in the DA-denervated striatum under the conditions of both PD with

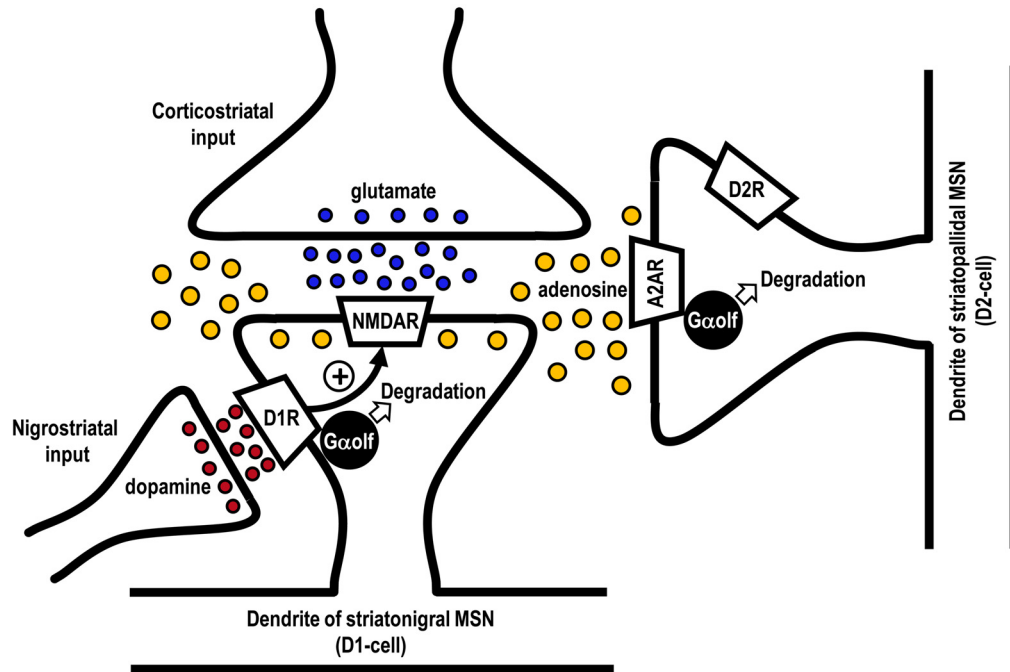


FIGURE 3 | Possible mechanism for agonist-induced degradation of $G\alpha_{olf}$ proteins in striatonigral and striatopallidal MSNs. Glutamate released from the corticostriatal afferents could activate postsynaptic *N-methyl-D-aspartate* (NMDA) receptors (NMDARs) to increase the extracellular adenosine levels in the striatum. Repeated exposure to levodopa might cause a pulsatile release of DA from the nigrostriatal afferents to activate DA D_1 receptors (D_1 R)s in striatonigral MSNs (D_1 -cells). This might facilitate the NMDAR-evoked increase in extracellular adenosine release and, thereby, indirectly activate the adenosine A_{2A} receptors (A_{2A} R)s in striatopallidal MSNs expressing DA D_2 receptors (D_2 R)s; D_2 -cells). Thus, a usage-induced downregulation of $G\alpha_{olf}$ protein levels could occur not only in the striatonigral MSNs but also in striatopallidal MSNs.

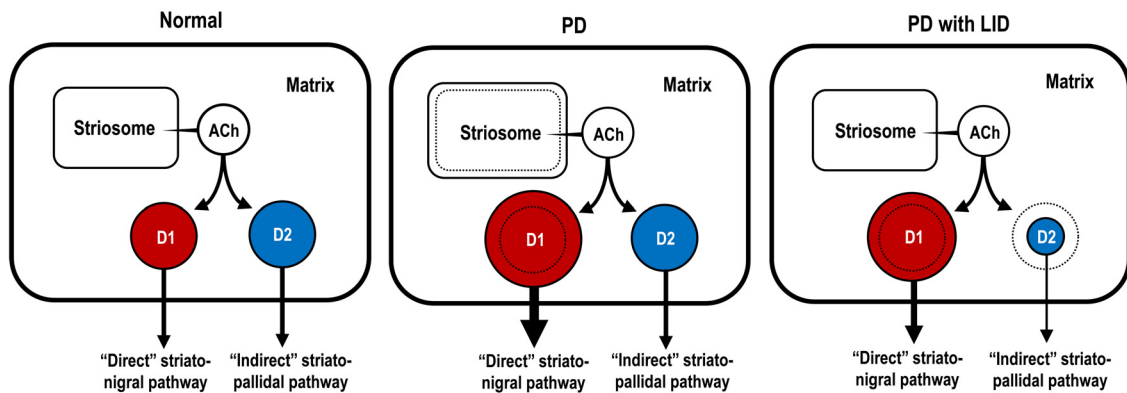


FIGURE 4 | Hypothetical diagram for dopaminergic regulation of $G\alpha_{olf}$ protein levels in striatonigral and striatopallidal MSNs. The sizes of the circles, colored in red and blue, indicate the abundance of $G\alpha_{olf}$ proteins in striatonigral MSNs expressing dopamine D_1 receptors (D_1 R)s; D_1 -cells; red) and in striatopallidal MSNs expressing dopamine D_2 receptors (D_2 R)s; D_2 -cells; blue), respectively. In the conditions of Parkinson's disease (PD), D_1 -cells, but not D_2 -cells, might exhibit a DA D_1 hypersensitivity caused by a dramatic increase in their $G\alpha_{olf}$ levels. In the conditions of PD with levodopa-induced dyskinesia (LID), D_1 -cells might show an increase in their $G\alpha_{olf}$ levels, while D_2 -cells might show a decrease in their $G\alpha_{olf}$ levels, which might result in an enhanced responsiveness to D_2 R activation. ACh, acetylcholine; D_1 -cell, striatonigral medium spiny neuron expressing DA D_1 receptor; D_2 -cell, striatopallidal medium spiny neuron expressing DA D_2 receptor; PD, Parkinson's disease; PD with LID, Parkinson's disease with levodopa-induced dyskinesia.

and without LID. In PD, there is a dramatic increase in the $G\alpha_{olf}$ protein levels in the striatonigral MSNs, but not in the striatopallidal MSNs. Because of no apparent changes in

the striatal D_1 R levels (Shinotoh et al., 1993; Turjanski et al., 1997; Hurley et al., 2001) and other principal mediators of the D_1 R signaling cascades (Girault et al., 1989; Nishino et al., 1993)

in patients with PD, the marked increase in the $G\alpha_{olf}$ protein levels in the striatonigral MSNs may be a principal cause for generating striatal D_1R hypersensitivity to levodopa exposure in PD. This notion corroborates the evidence that there is a marked increase in the responsiveness of the striatonigral MSNs to D_1R activation in PD, as determined by the fos induction experiments (Engber et al., 1989; Asin et al., 1995; Kashihara et al., 2000; Xu et al., 2003; Morigaki et al., 2017).

In PD with LID, there is an important decrease in the $G\alpha_{olf}$ protein levels in the striatopallidal MSNs after a prolonged and pulsatile administration of levodopa. This leads to the facilitation of the effects of DA on striatopallidal MSNs by reducing the $A_{2A}R/G\alpha_{olf}$ signal-mediated cAMP production and subsequently to the increase in the responsiveness of striatopallidal MSNs to D_2R activation. Indeed, it was importantly noted that, during the increasing phase of dyskinesias, an abnormal lowering of intracellular cAMP levels transiently occurred in the DA-denervated striatum in rat model of LID (Sancesario et al., 2014). These novel findings parallel the evidence that a repeated exposure to levodopa results in a significant increase in the responsiveness of striatopallidal MSNs to dopaminergic stimulation, as determined by fos induction experiments (Engber et al., 1989; Asin et al., 1995; Kashihara et al., 2000; Xu et al., 2003; Morigaki et al., 2017). In addition, there is a significant increase in the $G\alpha_{olf}$ protein levels in striatonigral MSNs in PD with LID as compared to normal controls. Because $G\alpha_{olf}$ is the regulator of cAMP signal-dependent activities in the striatum, an increase in the responsiveness of both striatonigral and striatopallidal MSNs to levodopa exposure, which depends on the $G\alpha_{olf}$ protein levels, serves as a principal cause for generating LID.

CONCLUDING REMARKS

Since the intracellular cAMP signaling cascades serve as a determinant of striatal cell activities (Girault, 2012), maladaptive change in $G\alpha_{olf}$ protein levels is thought to be closely linked to the pathophysiology of PD (Hervé, 2011). Here, we hypothesized that DA depletion might cause a marked upregulation of the $G\alpha_{olf}$ protein levels in striatonigral MSNs, which results in a crucial hypersensitivity of the striatum to D_1R stimulation in PD. A *prolonged* and *pulsatile* exposure to levodopa might lead to a usage-dependent decrease in the $G\alpha_{olf}$ protein levels not only in the nigrostriatal MSNs but also in the striatopallidal MSNs in PD with LID. This levodopa-induced decrease in $G\alpha_{olf}$ protein levels, which might be due to a *pulsatile* activation of postsynaptic D_1Rs and NMDA receptors, could result in reduced $A_{2A}R/G\alpha_{olf}/cAMP$ signal levels in striatopallidal MSNs. This might cause an increase in the responsiveness of striatopallidal MSNs to D_2R activation, and thereby develop LID in PD. Our hypothesis corroborates the long-lasting concept that LIDs are associated with a decreased activity of the “indirect” striatopallidal pathway (Crossman, 1990; DeLong, 1990; Brotchie, 2005).

As an important cellular mechanism to regulate the activities of striatal MSNs, the recurrent collateral connections between

the MSNs have also been identified (Bolam et al., 1983; Yung et al., 1996). The activities of striatopallidal MSNs can be inhibited by the GABAergic collateral axon branches from neighboring MSNs (Taverna et al., 2008; Lalchandani et al., 2013; Dobbs et al., 2016; Wei et al., 2017). Thus striatal D_1 hypersensitivity could lead to an increased responsiveness of striatopallidal MSNs to D_2R activation in the conditions of PD with and without LID, although only a small population of the striatonigral MSNs has been found to form collateral axon connections with striatopallidal MSNs in the mouse striatum (Taverna et al., 2008). However, this notion *per se* could not explain the progressive increase in the severity of LID, which occurs in the PD patients treated with unaltered dosages of given dopaminergic drugs (Brotchie, 2005), because there is an ongoing decline in striatal responsiveness to D_1R activation along a repeated exposure to levodopa under the conditions of PD, as determined by fos induction experiments (Saka et al., 1999; Kashihara et al., 2000; Xu et al., 2003; Morigaki et al., 2017).

Finally, we suggest that the pharmacological concomitant therapy to increase $G\alpha_{olf}$ protein levels in the striatum might be useful in the management of LID and motor fluctuations in patients with PD treated with DA replacement therapy. The normalization of the decreased $G\alpha_{olf}$ protein levels in the striatopallidal MSNs might suppress LID. On one hand, the elevation of the $G\alpha_{olf}$ protein levels in the striatonigral MSNs could increase the striatal responsiveness to D_1R activation and, thereby, facilitate the therapeutic efficacy of dopaminergic drugs. In considering the possible involvement of the activated NMDA receptors in lowering striatal $G\alpha_{olf}$ levels in LID, NMDA receptor antagonists (e.g., amantadine or memantine) might attenuate LID, as already shown in clinical practice (Rascol et al., 2015). Because $A_{2A}R$ activation, which could reduce the $G\alpha_{olf}$ protein levels in the striatopallidal MSNs leading to LID, might be required for the “priming” of LID (Brotchie, 2005; Xiao et al., 2006), it is suggested that $A_{2A}R$ antagonists (e.g., istradefylline) might be effective in dampening the “priming” of LID. However, after the establishment of LID, the adjunct use of $A_{2A}R$ antagonists might exacerbate the dyskinetic symptoms as shown in clinical practice (Kondo and Mizuno, 2015).

AUTHOR CONTRIBUTIONS

SG wrote the manuscript.

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