Striatal $G_{\text{olf}}^{\alpha}$/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 $\alpha$ subunit ($G_{\text{olf}}^{\alpha}$) represents an important regulator of the cAMP signal activities in the striatum, where it positively couples with $D_1$-type dopamine receptor ($D_1$R) and adenosine $A_{2A}$ receptor ($A_{2A}$R) to increase cAMP production in the MSNs. Notably, $D_1$Rs are primarily expressed in striatonigral MSNs, whereas $D_2$Rs and $A_{2A}$Rs are expressed in striatopallidal MSNs. Based on the evidence obtained from parkinsonian mice, we hypothesized that in the DA-denervated striatum with $D_1$R hypersensitivity, a repeated and pulsatile exposure to levodopa might cause a usage-induced degradation of $G_{\text{olf}}^{\alpha}$ proteins in striatal MSNs, resulting in increased and decreased levels of $G_{\text{olf}}^{\alpha}$ 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.

Keywords: olfactory type G-protein $\alpha$ subunit, levodopa-induced dyskinesia, Parkinson’s disease, dopamine, striatum

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). $G_{\alpha}$ is the
predominant stimulatory G-protein subunit in the brain. However, in the striatum, G\textsubscript{olf} is replaced by the olfactory type G protein \(\alpha\) subunit (G\textsubscript{olf}), which is encoded by the GNAL gene (Jones and Reed, 1989). Cellular G\textsubscript{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 (Jones and Reed, 1989). Cellular G\textsubscript{olf} is highly expressed in all striatal MSNs including those expressing the D\textsubscript{1}Rs and A\textsubscript{2A}Rs (Kull et al., 2000; Hervé, 2011; Morigaki et al., 2017; see Figure 2). As G\textsubscript{olf} positively couples with D\textsubscript{1}Rs and A\textsubscript{2A}Rs 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\textsubscript{1}R- and A\textsubscript{2A}R-dependent cAMP production in striatal MSNs (Kull et al., 2000; Corvol et al., 2001). The G\textsubscript{olf} protein level plays a key role in regulating the D\textsubscript{1}R/cAMP- and A\textsubscript{2A}R/cAMP-signal activities of striatonigral and striatopallidal MSNs, respectively. The D\textsubscript{1}R/G\textsubscript{olf}-mediated increases in the cAMP levels cause the activation of the striatonigral MSNs (Hervé, 2011). On one hand, as D\textsubscript{2}R activation inhibits AC5 through G\textsubscript{i/0} proteins but A\textsubscript{2A}R activation elicits AC5 through G\textsubscript{olf} proteins (Kull et al., 2000), the A\textsubscript{2A}R/G\textsubscript{olf}-signal stimulation functionally opposes the actions of D\textsubscript{2}Rs on the striatopallidal MSNs (Schwarzchild et al., 2006; Fuxe et al., 2007).

**SUBDIVISIONAL AND COMPARTMENTAL LOCALIZATION OF G\textsubscript{olf} IN THE STRIATUM**

Quantitative immunohistochemistry (IHC) has shown that the G\textsubscript{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\textsubscript{olf} protein indicates that G\textsubscript{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\textsubscript{olf} with higher densities of G\textsubscript{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\textsubscript{olf} may be a key molecule that determines differential responses between the striosome and matrix compartments to the D\textsubscript{1}R or A\textsubscript{2A}R activation in the striatum at maturity.

**HOMEOSTATIC REGULATION OF THE CELLULAR G\textsubscript{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\textsubscript{olf}. In...
line with the evidence that there is a significant increase in G\textsubscript{olf} protein levels in the putamen of patients with PD (Corvol et al., 2004), a dramatic increase in G\textsubscript{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 $D_1$Rs 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 $D_1$Rs 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 $D_1$Rs (Hervé et al., 2001; Corvol et al., 2004, 2007; Alcacer et al., 2012; Ruiz-DeDiego et al., 2015) or $A_3A$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 $D_1$Rs 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 $D_1$Rs, 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 $D_1$Rs. 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 $D_1$Rs 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\(_1\)Rs) in striatonigral MSNs (D1-cells). This might facilitate the NMDAR-evoked increase in extracellular adenosine release and, thereby, indirectly activate the adenosine A\(_{2A}\) receptors (A\(_{2A}\)Rs) in striatopallidal MSNs expressing DA D\(_2\) receptors (D\(_2\)Rs; D2-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\(_1\)Rs; D1-cells; red) and in striatopallidal MSNs expressing dopamine D\(_2\) receptors (D\(_2\)Rs; D2-cells; blue), respectively. In the conditions of Parkinson’s disease (PD), D1-cells, but not D2-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), D1-cells might show an increase in their G\(_{\alpha}\)olf levels, while D2-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; D1-cell, striatonigral medium spiny neuron expressing DA D\(_1\) receptor; D2-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 \( \text{G}_{\alpha_{olff}} \) protein levels in the striatonigral MSNs may be a principal cause for generating striatal \( \text{D}_1 \)R 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 \( \text{D}_1 \)R 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 \( \text{G}_{\alpha_{olff}} \) 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 \( \text{A}_2 \alpha \text{R}/\text{G}_{\alpha_{olff}} \) signal-mediated cAMP production and subsequently to the increase in the responsiveness of striatopallidal MSNs to \( \text{D}_1 \)R 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 (Sanesario 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 \( \text{G}_{\alpha_{olff}} \) protein levels in striatonigral MSNs in PD with LID as compared to normal controls. Because \( \text{G}_{\alpha_{olff}} \) 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 \( \text{G}_{\alpha_{olff}} \) 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 \( \text{G}_{\alpha_{olff}} \) 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 \( \text{G}_{\alpha_{olff}} \) protein levels in striatonigral MSNs, which results in a crucial hypersensitivity of the striatum to \( \text{D}_1 \)R stimulation in PD. A prolonged and pulsatile exposure to levodopa might lead to a usage-dependent decrease in the \( \text{G}_{\alpha_{olff}} \) protein levels not only in the nigrostriatal MSNs but also in the striatopallidal MSNs in PD with LID. This levodopa-induced decrease in \( \text{G}_{\alpha_{olff}} \) protein levels, which might be due to a pulsatile activation of postsynaptic \( \text{D}_1 \)Rs and NMDA receptors, could result in reduced \( \text{A}_2 \alpha \text{R}/\text{G}_{\alpha_{olff}}/\text{cAMP} \) signal levels in striatopallidal MSNs. This might cause an increase in the responsiveness of striatopallidal MSNs to \( \text{D}_2 \)R 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 (Grossman, 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; Lalchanandi et al., 2013; Dobbs et al., 2016; Wei et al., 2017). Thus striatal \( \text{D}_1 \) hypersensitivity could lead to an increased responsiveness of striatopallidal MSNs to \( \text{D}_2 \)R 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 \( \text{D}_1 \)R 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 \( \text{G}_{\alpha_{olff}} \) 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 \( \text{G}_{\alpha_{olff}} \) protein levels in the striatopallidal MSNs might suppress LID. On one hand, the elevation of the \( \text{G}_{\alpha_{olff}} \) protein levels in the striatonigral MSNs could increase the striatal responsiveness to \( \text{D}_1 \)R activation and, thereby, facilitate the therapeutic efficacy of dopaminergic drugs. In considering the possible involvement of the activated NMDA receptors in lowering striatal \( \text{G}_{\alpha_{olff}} \) 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 \( \text{A}_2 \alpha \text{R} \) activation, which could reduce the \( \text{G}_{\alpha_{olff}} \) 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 \( \text{A}_2 \alpha \text{R} \) antagonists (e.g., istradefylline) might be effective in dampening the “priming” of LID. However, after the establishment of LID, the adjunct use of \( \text{A}_2 \alpha \text{R} \) 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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**Conflict of Interest Statement:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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