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Glutamate-mediated striatal dysregulation and the pathogenesis of motor response complications in Parkinson's disease

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Summary. Chronically administered levodopa to Parkinson's disease (PD) patients ultimately produces alterations in motor response. Similarly, in 6-hydroxydopamine lesioned hemiparkinsonian rats, chronic twice-daily administration of levodopa progressively shortens the duration of contralateral turning, an index of, the wearing-off fluctuations that occur in parkinsonian patients. The pathogenesis of these response alterations involves, in part, upregulation of corticostriatal glutamatergic synaptic transmission. Changes involving kinase and phosphatase signaling pathways within striatal dopaminoceptive medium-spiny neurons now appear to contribute to increased synaptic efficacy of glutamatergic receptors in these neurons. Glutamate-mediated striatal sensitization subsequently modifies basal ganglia output in ways that favor the appearance of parkinsonian motor complications. At the molecular level, transcriptional activation of striatal CREB and cdk5 may contribute to the persistent expression of these levodopa-induced response alterations. Conceivably, a safer and more effective therapy for PD can be provided by drugs that target signaling proteins within striatal spiny neurons or those that interact extracellularly with non-dopaminergic receptors such as AMPA and NMDA, adenosine, adrenergic, opioid, and serotonergic.

Keywords: NMDA receptor – AMPA receptor – Medium spiny neuron – Phosphorylation – Signal transduction

Introduction

The cardinal signs of Parkinson's disease (PD) reflect striatal dopamine (DA) depletion due to degeneration of the nigrostriatal dopaminergic pathway (Guttman et al., 1997, Hornykiewicz, 1998). These motor deficits, which include tremor, rigidity, and bradykinesia, initially respond well to drugs such as levodopa or DA agonists that restore normal dopaminergic transmission. Within a few years, however, treatment with dopaminomimetics begin to produce adverse motor responses including motor fluctuations and dyskinesias (Miyawaki et al., 1997; Quinn et al., 1998).

These disabling complications appear to reflect the non-physiological stimulation of striatal DA receptors, initially as a consequence of the wide fluctuations in synaptic DA produced by conventional levodopa therapy in advanced patients (Bedard et al., 1995; Blanchet et al., 1995; Jenner et al., 2000; Chase et al., 1998). Indeed, these response alterations can be alleviated or prevented by drugs or dosing regimens that provide essentially continuous, and thus more physiological, DA receptor stimulation (Mouradian et al., 1990; Chase et al., 1994; Chase and Oh, 2000a). Parkinsonian rodents or nonhuman primates (Engber et al., 1994; Papa et al., 1996) treated with levodopa manifest similar motor response changes. For instance, rats rendered parkinsonian by the injection of 6-hydroxydopamine and then treated twice daily with levodopa develop a progressive shortening in response duration which underlies the wearing-off fluctuations occurring in PD patients (Papa et al., 1994). Similarly, monkeys lesioned with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) develop wearing-off fluctuations as well as choreiform and dystonic dyskinetic movements after a few weeks of daily levodopa treatment (Papa et al., 1996; Clarke et al., 1987; Blanchet et al., 1998). These abnormal involuntary movements closely resemble these occurring in patients with advanced PD who are receiving dopaminomimetic therapy.

Animal model studies such as these suggest that changes in striatal output due to medium-sized spiny

neuron dysregulation may contribute to the pathogenesis of the motor complication syndrome (Bravi et al., 1994; Chase et al., 1998). Medium spiny neurons are the preponderant nerve cell in the striatum. They receive synaptic input from the dopaminergic nigrostriatal and glutamatergic corticostriatal pathways as well as a number of other systems both intrinsic and extrinsic to the striatum and project to the major output nuclei of the basal ganglia, the internal segment of the globus pallidus and the pars reticulata of the substantia nigra (Gerfen et al., 1992; Graybiel et al., 1994; Kotter, 1994). Their operational state is thus a critical determinate of motor behavior including certain of the plastic responses associated with basal ganglia function (Calabresi et al., 1996; Cervo et al., 1996).

Role of glutamatergic receptors in motor response complications

Considerable need exists for the development of improved treatments for patients with advanced PD in relation to preventing or ameliorating the motor symptoms resulting not only from dopaminergic human degeneration but also from chronic levodopa treatment. Of particular importance in this regard has been the exploration of the therapeutic potential of drugs that selectively interact with striatal glutamatergic systems.

Recent evidence from parkinsonian animal (Oh et al., 1998, 1999; Dunah et al., 1999; Chase and Oh, 2000b) and patient (Blanchet et al., 1998; Metman et al., 1998b) studies indicates that nonphysiological stimulation of DA receptors on striatal spiny neurons leads to changes in the subunit phosphorylation pattern of coexpressed ionotrophic glutamatergic receptors: N-methyl-D-aspartate (NMDA) subtype and amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) subtype receptors. As a result, these receptors undergo an increase in synaptic efficacy in ways that favor the appearance of response alterations produced by levodopa treatment.

The results of earlier studies in parkinsonian rats appear consistent with this possibility, since NMDA receptor antagonists, such as MK801, were found to act palliatively and prophylactically to decrease response alterations (Engber et al., 1994; Marin et al., 1996; Papa et al., 1995; Cepeda et al., 1998). Subsequent observations in parkinsonian primates have provided additional support for this hypothesis. Co-administration of various NMDA antagonists to these animals substantially reduced the dyskinesiogenic effects of levodopa (Gomez-Mancilla et al., 1993; Papa et al., 1995, 1996; Blanchet et al., 1997, 1998). Similarly, studies in parkinsonian patients given NMDA receptor antagonists, such as dextrorphan, dextromethorphan or amantadine, indicate that drugs of this type can alleviate motor fluctuations as well as peak dose dyskinesias (Blanchet et al., 1996; Danysz et al., 1997; Mitchell et al., 1997; Metman et al., 1998a,b,c; Karcz-Kubicha et al., 1998; Del Dotto et al., 2001).

Functional alterations in glutamate receptors other than those of the NMDA subtype may also contribute to levodopa-induced motor dysfunction in advanced PD. For example, administration of the competitive AMPA receptor antagonist, NBQX, to parkinsonian rats or monkeys reportedly has little or no effect on motor function, but can potentiate the antiparkinsonian action of levodopa (Klockgether et al., 1991; Luquin et al., 1993). In rats, NBQX also acts to reverse levodopa-associated motor response alterations (Marin et al., 2000). In primates, a selective, noncompetitive antagonist at the AMPA allosteric modulation site (LY 300164) alone did not modify the severity of parkinsonian signs, but did attenuate levodopa-induced dyskinesias. Conversely, a selective AMPA agonist (CX516) by itself had no antiparkinsonian activity, but potentiated levodopa-associated dyskinesias (Chase et al., 2000; Konitsiotis et al., 2000). Taken together, these data suggest that treatment with NMDA or AMPA receptor antagonists might have beneficial effects on response complications associated with levodopa treatment.

Glutamate-mediated striatal dysregulation and motor response complications

Recent studies have provided increasing insight into how phosphorylation changes in striatal glutamatergic receptors may occur in response to chronic, nonphysiological dopaminergic stimulation. It now appears that alterations in the phosphorylation state of striatal NMDA and AMPA receptors reflect the aberrant activation of signaling cascades linking DA and glutamate receptors expressed along the denderites of medium spiny neurons (Chase et al., 1998; Chase and Oh, 2000a). More specifically, changes in the balance between specific spiny-neuron kinase and phosphotase activity appear to affect the degree and pattern of phosphorylation (Chase et al., 1998; Oh et al., 1997, 1998; Chase and Oh, 2000b).

With respect to NMDA receptors, current evidence suggests that the chronic non-physiological stimulation of rat DA receptors activates various kinases responsible for direct subunit phosphorylation (Oh et al., 1997, 1998, 1999; Dunah et al., 2001) as well as for synaptic clustering (Ulas et al., 1996; Dunah et al., 2001). These include serine kinases, such as cyclic AMP-protein kinase A (PKA), calcium/calmodulin-dependent protein kinase II (CaMKII), and calcium-activated protein kinase (PKC), as well as src or fyn tyrosine kinases (Menegoz et al., 1995; Oh et al., 1997, 1998, 1999; Suen et al., 1998; Greengard et al., 1999; Bayer et al., 2001; Lan et al., 2001; Liao et al., 2001b). The intrastriatal administration of inhibitors of certain of these serine and tyrosine kinases alleviates the motor response alterations (Oh et al., 1997, 1998, 1999).

In various animal models of learning and memory (Oh et al., 1998), a rise in the sensitivity of glutamatergic receptors, especially those of the NMDA subtype, appears to contribute to the persisting, activity-dependent changes in neuronal responses (Nicoll et al., 1995; Cain et al., 1997). NMDA receptors are heteroligomers assembled to form ligand-gated ion channels from one or two NR1 subunits, expressed in eight currently recognized splice variants (a–h), and two or three NR2 subunits composed of four homologous isoforms (A–D) (Wollmuth et al., 1996; Ozawa et al., 1998). In rat striatum, medium spiny neurons express NR1 variants along with NR2B and, to a lesser extent, NR2A subunits (Chen et al., 1996). Protein phosphorylation serves as a major regulatory mechanism for these receptors (Gurd et al., 1997; Suen et al., 1998). The phosphorylation of tyrosine residues has been reported to modulate channel opening probability (Yu et al., 1997; Wang et al., 1998) and receptor trafficking to the postsynaptic membrane (Dunah et al., 2001), while serine/threonine phosphorylation by calcium/phospholipid-stimulated or cAMP-stimulated protein kinases appears to affect their subcellular distribution, plasma membranes anchoring (Hisatsune et al., 1997; Tingley et al., 1997) and synaptic clustering (Crump et al., 2001). Recently, PKC has also been shown to influence NMDA currents by direct serine phosphorylation of the NR2B tail at residues S1303 and S1323 (Liao et al., 2001b) or by direct tyrosine phosphorylation of the NR2A and NR2B subunits (Grosshans et al., 2001).

With respect to striatal AMPA receptor subunits, changes in the phosphorylation state of serine residues by a PKC signaling cascade may also affect motor function. Preliminary results indicate that an abundance of constitutively active PKC as a consequence of striatal pCMVpkc gene transfer may be sufficient to promote the initial appearance of levodopa-induced motor response alterations, in part, by the phosphorylation of AMPA receptor subunits (Liao et al., 2001a, Snyder et al., 2001) and consequent modification of the strength of corticostriatal glutamatergic input. Taken together, differential activation of signal transduction pathways within spiny neurons lead to characteristic changes in the phosphorylation state of NMDA and AMPA glutamate receptors and thus in their sensitivity to corticostriatal synaptic input. As a consequence of these molecular and cellular events, striatal output changes in ways that contribute to the motor complications associated with levodopa therapy. Prevention or reversal at the level of the intracellular signaling alterations could thus prove therapeutically useful.

Role of non-glutamatergic receptors in motor response complications

Spiny-neurons express numerous non-glutamatergic and non-dopaminergic receptors that also make an important contribution to the functional state of these striatal GABAergic output neurons. These cell surface receptors include adenosine A2a, serotonergic 5HT2A, adrenergic alpha-2a, and opioid Mu or Kappa (Hughes et al, 1998; Kanda et al., 1998; Jenner et al., 2000 ; Jimennez et al., 2000; Grondin et al., 2000; De Deurwaerdere et al., 2000; Johansson et al., 2001; Bibbiani et al., 2000; Fox et al., 2001). Mounting clinical and preclinical evidence suggests that drugs which interact with these receptors can potentially affect motor dysfunction associated with dopaminergic therapy in animal models of PD (Jenner et al., 2000; Grondin et al., 2000; Johansson et al., 2001; Bibbiani et al., 2001). Whether or not these receptors act by modulating the phosphorylation state and thus the synaptic efficacy of striatal spiny neurons has yet to be determined. Nevertheless, it is conceivable that the selective targeting of striatal non-glutamatergic receptors could prove to be an efficacious approach to the restoration of spiny neuron dysfunction associated with the nonphysiological stimulation of the DA receptors.

Many of these striatal non-glutamatergic receptors are linked to G-protein signaling cascades. Con-

ceivably, their activation might thus contribute to the synaptic sensitivity of coexpressed glutamatergic receptors. Indeed, recent findings suggest that the administration of the adenosine A2a receptor antagonist, KW-6002, which has been shown to diminish levodopa-induced motor complications (Kanda et al., 1998; Jenner et al., 2000), normalizes both the shortened response to levodopa in parkinsonian rats and, concomitantly, the augmented serine phosphorylation (S831) of striatal AMPA receptor GluR1 subunits (Oh JD, unpublished observation). Amantadine's benefit in treating motor response complications (Blanchet et al., 1998; Metman et al., 1998b; Karcz-Kubicha et al., 1998; Del Dotto et al., 2001) might also relate, in part, to an attenuation of the heightened phosphorylation of striatal glutamatergic receptor subunits (serine phosphorylation of NR1 and tyrosine phosphorylation of NR2B) caused by chronic levodopa therapy (Oh JD, unpublished observation). Pharmaceutical agents selectively acting on these receptors might thus provide a novel and safer approach to treating motor complications in advanced PD patients.

Molecular mechanisms

Molecular and cellular mechanisms underlying the development, expression, and maintenance of long-lasting motor response alterations induced by chronic dopaminomimetic therapy may also involve changes in the balance between striatal kinase and phosphatase activity (Oh et al., 1997; Chase et al., 1998; Khan et al., 1999). Onset of levodopa-induced response changes can take only a few weeks in parkinsonian animals and PD patients (Chase et al., 1998; Mouradian et al., 1990). Offset time also is similar in animal models and in patients with motor complications: in either case, the altered responses persist for several weeks following withdrawal of intermittent dopaminomimetic treatment or conversion to more physiologic continuous administration (Mouradian et al., 1990). Levodopa-induced motor response complications thus possess features characteristic of long term memory – longevity and reversibility.

Chronic intermittent levodopa administration also alters the expression of various striatal transcriptional factor (Cenci et al., 1998, 1999; Chase et al., 1998; Khan et al., 1999) and neuropeptide (Engber et al., 1991; Herrero et al., 1995; Morissette et al., 1996; Parent et al., 1996; Ferraro et al., 1998; Henry et al., 1999) genes. One such transcription factor, that has been linked to striatal DA receptors and has been implicated in the long-term maintenance of synaptic plasticity elsewhere in the CNS (Bartsch et al., 1998; Impey et al., 1998; Ahn et al., 1999), is cAMP response element-binding protein (CREB) (Cervo et al., 1996; Gurd et al., 1997; Graybiel et al., 1998; Huang et al., 1998; Silva et al., 1998).

Since the late phase of memory appears to depend on new transcription and translation (Pittenger et al., 1998), CREB might act by regulating the synthesis of proteins involved in these consolidation processes. CREB is a member of a large family of structurally related transcription factors which binds to cAMP-response-element (CRE) promoter sites on target genes (Ginty et al., 1997). CREB protein, which can exist in multiple alternatively spliced isoforms in rat CNS (Pietruck et al., 1999), has been implicated in the transcriptional regulation of a number of genes (Pietruck et al., 1999), especially those which are rapidly expressed in response to elevations in cytoplasmic cAMP (Quinn et al., 1993) and Ca^{2+} (Ginty et al., 1997; Hu et al., 1999). Similar to such other inducible transcription factors as Jun and Fos, CREB protein has several functional domains – a leucine zipper domain which mediates dimerization, a DNA binding domain, and a transcriptional activation domain which contains crucial phosphorylation sites (Quinne et al., 1998; Pietruck et al., 1999). The transcriptional activation of CREB depends on its phosphorylation at Ser-133 either directly or indirectly by such kinases as PKA and CaMK (Gonzalez et al., 1991; Sheng et al., 1991; Das et al., 1997; Hu et al., 1999). Preliminary results suggest that striatal DA receptor-activated PKA/CREB-mediated mechanisms contribute to the development and maintenance of the motor response changes associated with levodopa treatment of parkinsonian rats (Oh JD; unpublished observation).

Levodopa-induced motor response alterations may also involve compensatory neural and behavioural adaptations, similar to those observed with psychoactive drug addiction, by counterbalancing the effects of repeated intermittent dopaminomimetic stimulation. Delta FosB is a transcription factor which has been implicated in compensatory neural and behavioral adaptations associated with repeated drug treatment. Its elevated expression in the striatum has been shown to be linked to chronic cocaine-induced alterations (Hope et al., 1994; Kelz et al., 1999; Bibb et al., 2001) as well as to chronic levodopa-induced striatal dysregulation (Andersson et al., 1999). A recent study

has identified Cdk5 as a downstream target gene of ΔFosB, and, upon activation, Cdk5 controls the efficacy of dopaminergic PKA signaling via positive feedback mechanisms in a mutually antagonistic manner (Lew et al., 1994; Nishi et al., 2000). Preliminary observations indicate that chronic non-physiological stimulation of striatal DA receptors in parkinsonian rats augments striatal Cdk5/p35 immune complex formation, Cdk5 activation, and DARPP-32-Thr-75 phosphorylation (Oh JD; unpublished observation). These results support the possibility that striatal DA receptor-activated Cdk5 may be involved in adaptive mechanisms occurring when repeated nonphysiological DA receptor stimulation produces certain long-term consequences leading to the motor response complications associated with levodopa therapy.

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