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Thomas N. Chase
Justin D. Oh
Spyridon Konitsiotis

Antiparkinsonian and antidyskinetic activity of drugs targeting central glutamatergic mechanisms

T. N. Chase (✉) · J. D. Oh · S. Konitsiotis
Experimental Therapeutics Branch, National Institute of Neurological Disorders and Stroke NIH, Building 10, Room 5C211, 10 Center Drive, MSC/406, Bethesda, MD 20892, USA
E-mail: Chase@helix.nigh.gov
Tel.: 001 301 496 7993
Fax: 001 301 496 6609

Abstract Motor dysfunction produced by the chronic non-physiological stimulation of dopaminergic receptors on striatal medium spiny neurons is associated with alterations in the sensitivity of glutamatergic receptors, including those of the N-methyl-D-aspartate (NMDA) subtype. Functional characteristics of these ionotropic receptors are regulated by their phosphorylation state. Lesioning the nigrostriatal dopamine system of rats induces parkinsonian signs and increases the phosphorylation of striatal NMDA receptor subunits on serine and tyrosine residues. The intrastriatal administration of certain inhibitors of the kinases capable of phosphorylating NMDA receptors produces a dopaminomimetic motor response in these animals. Treating parkinsonian rats twice daily with levodopa induces many of the characteristic features of the human motor complication syndrome and further increases the serine and tyrosine phosphorylation of specific NMDA receptor subunits. Again, the intrastriatal administration of selective inhibitors of certain serine and tyrosine kinases alleviates the motor complications. NMDA receptor antagonists, including some non-competitive channel blockers, act both palliatively and prophylactically in rodent and primate models to reverse these levodopa-induced response alterations. Similarly, in clinical studies dextrorphan, dextromethorphan, and amantadine have been found to be efficacious against motor complications. Recent observations in animal models further indicate that certain amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) antagonists alleviate, while others exacerbate, these complications. Thus, it appears that the denervation or intermittent stimulation of striatal dopaminergic receptors differentially activates signal transduction pathways in medium spiny neurons. These in turn modify the phosphorylation state of ionotropic glutamate receptors and consequently their sensitivity to cortical input. These striatal changes contribute to symptom production in Parkinson's disease, and their prevention or reversal could prove useful in the treatment of this disorder.

Key Words AMPA receptor · Medium spiny neuron · NMDA receptor · Phosphorylation · Signal transduction

Introduction

The cardinal signs of Parkinson's disease (PD) reflect alterations in striatal dopaminergic transmission. Tremor, rigidity, and bradykinesia result from an insufficiency of intrasynaptic dopamine (DA) and become clinically manifest when striatal levels of the transmitter decline by about 50% [13, 33, 57]. These motor abnormalities initially respond well to drugs such as levodopa or DA agonists that

improve dopaminergic transmission. Later, however, the response to pharmacological agents of this type becomes increasingly less satisfactory, mainly due to the appearance of treatment-refractory signs (gait and balance disorders, freezing, dementia, and affective changes) and various adverse events, especially motor response complications [18, 55]. Most commonly, these latter changes include various types of response fluctuations and dyskinesias [55, 69]. As in the case of parkinsonian signs, these ultimately disabling adverse events probably reflect the non-physiological stimulation of striatal DA receptors. In contrast to the chronic hypostimulation produced by DA system degeneration, however, it is the periodic hyperstimulation associated with most dopaminomimetic therapies that appears to favor the appearance of motor response complications.

Non-physiological stimulation of dopamine receptors

While it is easy to understand why dopaminergic denervation might alter downstream mechanisms in the basal ganglia, the basis for the reactive changes associated with standard dopaminomimetic therapies has only recently become clear. DA-containing neurons comprising the nigrostriatal system characteristically manifest slow (about 4–5 Hz), single-spike activity which is occasionally interrupted by short bursts of faster (usually in the 15–20 Hz range) spiking in response to salient visual or auditory stimuli [29, 71]. Since postsynaptic receptor stimulation is roughly proportional to impulse activity at the presynaptic terminal, intrasynaptic DA concentrations normally remain fairly constant. Accordingly, the most physiological approach to dopamine replacement in PD would be to maintain stable normal intrasynaptic levels of the transmitter amine; however, with disease progression, this goal becomes progressively less attainable. As nigral dopaminergic neurons degenerate, the amount of exogenous levodopa entering striatal terminals diminishes. Instead, increasing amounts are taken up and converted to DA in other decarboxylase-containing cells, especially serotonergic neurons [52, 59, 84]. In the absence of appropriate mechanisms for storing or regulating the release of DA, the newly synthesized amine leaks into the extracellular compartment and diffuses into nearby DA receptors. Under such circumstances, intrasynaptic DA concentrations reflect the wide swings in cerebral levodopa levels that occur with standard precursor dosing regimens. Levodopa therapy in patients with advanced PD thus results, at best, in only episodic restoration of physiological dopamine levels [9]. For most of the dosing cycle, with the administration of short-acting DA agonists at any stage of Parkinson's disease, or of levodopa in patients with advanced disease, dopaminergic receptor stimulation remains at subthreshold levels, interrupted soon after each dose when it briefly rises into the physiological range. Indeed, postmortem determinations of striatal DA concentrations, as well as clinical measurements of spinal fluid homovanillic acid levels (the major metabolite of DA), suggest that transmitter levels in parkinsonian patients receiving standard levodopa therapy ordinarily peak well above the physiological range, presumably at levels approximating to those achieved in in vitro models exposed to high-intensity (tetanic) stimulation [17, 37, 58]. With a sufficient loss of DA terminals, dopaminergic transmission thus tends to be compromised whether or not dopaminomimetic treatment is initiated.

It has now become increasingly clear that this non-physiological pattern of stimulation contributes to the appearance of the major motor complications associated with long-term levodopa or DA agonist administration. The nigrostriatal DA system terminates on the dendritic spines of the preponderant striatal nerve cell, the medium-sized spiny neuron [44]. Medium spiny neurons also receive glutamatergic axons descending from all areas of the cerebral cortex. In addition, they make synaptic contact with numerous other neuronal systems, both extrinsic (e.g., adrenergic and serotoninergic) and intrinsic (e.g., cholinergic and somatostatinergic) to the striatum. In turn, these GABAergic efferent neurons project, both directly and indirectly, to the major output nuclei of the basal ganglia, the internal segment of the globus pallidus and the pars reticulata of the substantia nigra [30, 73]. Medium spiny neurons, thus, serve as a major anatomical locus for the processing of cortical information through the basal ganglia. They also appear to contribute to certain plastic responses now associated with basal ganglia function [11, 16].

Increasing evidence suggests that the chronic non-physiological stimulation of DA receptors triggers adaptative responses in the striatum and other basal ganglionic structures. To date, these changes have largely been studied in animal models of PD. Rats rendered parkinsonian by the injection of 6-hydroxydopamine and then treated intermittently with levodopa (by twice-daily injection to simulate clinical conditions) develop progressive motor response alterations, which resemble the fluctuations occurring in similarly treated parkinsonian patients [67]. Daily measurements reveal a progressive shortening in response duration that becomes statistically significant within about 3 weeks. Thus, like parkinsonian patients, parkinsonian rats exhibit the wearing-off phenomenon. At the same time, they also show evidence of response alterations that mimic human on–off fluctuations. The frequency with which there is no response to an otherwise effective dose of levodopa rises, and the slope of the levodopa dose/motor response relation becomes steeper [49]. While parkinsonian rats develop motor fluctuations, under the conditions of these experiments they do not develop choreiform dyskinesias. In contrast to 6-hydroxydopamine-lesioned rats, cynomolgus monkeys lesioned with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) develop typical choreiform and dystonic movements within a few weeks of daily levodopa treatment [8, 48].

Peptide cotransmitters

Levels of the peptide cotransmitters used by medium spiny neurons can serve as reliable markers of their functional state. Several of these neuropeptides have been found to undergo characteristic alterations in parkinsonian rodents and primates as a result of denervation and subsequent levodopa therapy [25, 27, 34, 35, 56, 68]. Spiny neurons that predominantly express the D2 DA receptor subtype mainly project to the internal segment of the globus pallidus via the external globus pallidus and subthalamic nucleus, and they contain the neuropeptides enkephalin and neurotensin. Spiny neurons that primarily express D1 DA receptors largely project directly to the internal segment of the globus pallidus/pars reticulata of the substantia nigra, and contain dynorphin and neurotensin [27, 45]. Lesioning the DA system of rats with 6-hydroxydopamine increases striatal concentrations of both enkephalin and neurotensin [25]. Subsequent intermittent levodopa treatment at a dose sufficient to induce motor response alterations leads to additional changes, most notably a striking rise in dynorphin and neurotensin levels [23, 25]. At the same time, the expression of messenger ribonucleic acids (mRNAs) encoding for these neuropeptides also increases, suggesting that their concentration changes may be the result of accelerated synthesis [27]. Related pharmacological studies indicate that these peptide modifications reflect alterations in spiny neuron output which can influence extrapyramidal motor function [22, 26, 48].

Role of NMDA receptors in Parkinson's disease

The effects of non-physiological stimulation on synaptic plasticity have been extensively studied in various animal models of learning and behavior [62]. Early investigative attention focused largely on the ability of repetitive high-frequency (tetanic) stimulation to evoke long-term potentiation (LTP) in the hippocampus [38, 51, 85]. More recently, LTP-like phenomena have been found in cortical and subcortical areas which influence motor behavior [2, 12, 14]. In these model systems, considerable evidence suggests that a rise in the sensitivity of glutamatergic receptors, especially those of the N-methyl-D-aspartate (NMDA) subtype, contributes to the persisting, activity-dependent changes in neuronal responses [10, 60]. Since NMDA and DA receptors are co-expressed in close proximity along the distal dendrites of medium spiny neurons [43, 73], the foregoing preclinical observations prompted evaluations of the possibility that the non-physiological stimulation of DA receptors on these striatal neurons might enhance NMDA receptor sensitivity in ways that favor the clinical appearance of parkinsonism and long-lasting motor complications [15, 24, 65].

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) [64, 87]. In rat striatum, medium spiny neurons express NR1 variants along with NR2B and, to a lesser extent, NR2A subunits [19]. Protein phosphorylation serves as a major regulatory mechanism for these receptors [32, 75]. The phosphorylation of tyrosine residues has been reported to modulate channel characteristics, including opening probability [86, 88], while serine/threonine phosphorylation by calcium/phospholipid-stimulated or cAMP-stimulated protein kinases appears to affect their subcellular distribution and anchoring to plasma membranes [36, 79]. Recent studies of rat striatal NMDA receptors have revealed changes in both tyrosine and serine phosphorylation that are associated with the development of parkinsonism following nigrostriatal system destruction, as well as with the appearance of motor response alterations following intermittent levodopa therapy.

The phosphorylation of rat striatal NMDA receptors at tyrosine residues increases when 6-hydroxydopamine-induced parkinsonism becomes evident [53, 62], and to an even greater extent when the altered motor responses to levodopa appear [62]. Both nigrostriatal denervation and subsequent levodopa administration mainly affect striatal NR2B subunits, although levodopa treatment also augments NR2A subunit tyrosine phosphorylation. In agreement with previous observations [80], we have also found that lesioning with 6-hydroxydopamine selectively increases striatal NR2A protein expression. Subsequent intermittent levodopa administration normalized levels of NR2A subunits, but had no effect on NR2B expression [62]. In relation to serine phosphorylation, there are increases on striatal NR2A subunits when rats are lesioned with 6-hydroxydopamine, and these are further augmented when the animals show altered motor responses to levodopa [63]. Neither nigrostriatal pathway destruction nor levodopa administration affect the expression or serine phosphorylation of NR2B subunits. Since receptor channel function, and therefore calcium ion fluxes, at the NMDA receptor complexes reflect their phosphorylation state, it is not unreasonable to assume that the observed enhancement in tyrosine and serine phosphorylation contributes to their heightened sensitivity and thus to the motor dysfunction which accompanies dopaminergic denervation and dopaminomimetic therapy [63].

Phosphorylation changes affecting NMDA receptors on striatal spiny neurons presumably depend on intracellular signaling cascades linking them with nearby dopaminergic receptors. Both the nigral dopaminergic and cortical glutamatergic systems innervate the distal dendrites of medium spiny neurons [43, 73]. Glutamatergic excitatory projections terminate at the spine heads, where all three of the major glutamatergic receptor subtypes [NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) and kainate] are expressed [1, 40]. Dopaminergic terminals make synaptic contact on the spine necks,

within a micron of the glutamate receptors, as well as at more proximal sites [72]. This intimate anatomical arrangement affords the potential for close physiological interactions between dopaminergic and glutamatergic receptor-mediated mechanisms. Indeed, recent observations suggest that the non-physiological stimulation of rat DA receptors activates striatal kinases believed to be capable of directly phosphorylating NMDA receptor subunits [61–63]. These include serine kinases, such as cyclic AMP-protein kinase A (PKA) and calcium/calmodulin-dependent protein kinase II (CaMKII), as well as tyrosine kinases, which are as yet unidentified but are most likely to be members of the src or fyn families [42, 61–63, 76, 77, 88]. Intrastriatal injection of the PKA inhibitor, Rp-cAMPS, or the CaMKII inhibitor, KN-93, for example, reverses the motor response changes produced by intermittent levodopa therapy [61, 63]. At the same time, KN-93 has been shown to attenuate the enhanced serine phosphorylation of NMDA receptors produced by levodopa therapy [63]. With respect to tyrosine phosphorylation, striatal infusion of the tyrosine kinase inhibitor, genistein, normalizes both the tyrosine phosphorylation increases and the motor response changes associated with levodopa treatment. Conversely, the tyrosine phosphatase inhibitor, okadaic acid, potentiates these alterations [62]. The foregoing results support the possibility that sensitization of NMDA receptors on striatal spiny neurons resulting, at least in part, from heightened subunit phosphorylation contributes to the onset of parkinsonian signs as a consequence of dopaminergic denervation, as well as to the appearance of the response modifications associated with intermittent levodopa treatment. In either case, alterations in cortical glutamatergic input to the striatum presumably modify striatal output in ways that influence motor function.

Pharmacological evaluations of this possibility were initially based on the premise that if an increase in striatal NMDA receptor sensitivity played a role in the production of symptoms associated with dopaminergic denervation or levodopa treatment, then pharmacological blockade of these receptors should ameliorate the motor dysfunction. The results of early studies in parkinsonian rats appeared consistent with this possibility, since NMDA receptor antagonists, such as MK801, were found to act both palliatively and prophylactically to decrease response alterations [24, 49, 65]. Subsequent observations in parkinsonian primates provided additional support for this hypothesis. Co-administration of certain NMDA antagonists to these animals substantially reduced the dyskinesiogenic effects of levodopa [4, 7, 28, 66]. Similarly, studies in parkinsonian patients given NMDA receptor antagonists, such as dextrorphan, dextromethorphan or amantadine, indicated that drugs of this type can alleviate motor fluctuations as well as peak dose dyskinesias [6, 81–83]. Regarding the clinical appearance of parkinsonian signs, results from 6-hydroxydopamine-lesioned rodents [76] as well as MPTP-lesioned primates [5, 31, 54] indicate that some intrastriatally- or systemically administered NMDA antagonists possess antiparkinsonian activity. Similarly, the well-established symptomatic benefit conferred to mildly afflicted parkinsonian patients by amantadine suggests that NMDA receptor antagonists can act as clinically effective palliatives [21, 74]. The foregoing preclinical and clinical observations support the possibility that striatal NMDA receptor sensitization contributes to the characteristic motor dysfunction occurring with both dopaminergic denervation and levodopa therapy.

Role of AMPA receptors in Parkinson's disease

Recent observations suggest that functional alterations in glutamate receptors other than those of the NMDA type may also contribute to symptom production in PD. For example, the administration of the competitive AMPA receptor antagonist, NBQX, to parkinsonian rats or monkeys reportedly has little or no effect on motor function but potentiates the antiparkinsonian action of levodopa [41, 46, 47]. In rats, we have found that NBQX acts to reverse levodopa-associated motor response alterations [48]. In primates, a selective, non-competitive antagonist of 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 [43]. These animal model results suggest that alterations in AMPA receptor-mediated mechanisms contribute to the motor dysfunction associated with dopaminergic denervation and subsequent dopaminomimetic treatment. The same may be true for glutamate receptors in the metabotropic family. All three currently identified subtypes of these G-protein-coupled receptors are known to be expressed in the striatum [87]. Both group I and III metabotropic agonists have now been reported to induce contralateral rotation, similar to dopaminomimetics, in 6-hydroxydopamine lesioned rats [70, 39].

A complex series of events involving glutamate receptor-mediated mechanisms in the basal ganglia participate in the plastic changes in motor function that characteristically arise in parkinsonian patients, initially as a result of the loss of striatal dopaminergic innervation and later due to the intermittent high-intensity stimulation produced by most currently available dopaminomimetic therapies. Although drugs that prevent or reverse these changes might be expected to confer symptomatic benefit, considerable additional investigative effort will be required to determine the optimal sites of pharmaceutical intervention. In part, this will involve the precise elucidation of the relative contribution of factors, such as the activation of particular signal transduction cascades, the differential phosphorylation of glutamate receptor subunits, and the sensitization of glutamatergic receptor subtypes to their natural

ligand. It may also entail improving our understanding of the modulatory role played by other neuronal systems that make synaptic contact with critical neurons in the striatum and in downstream basal ganglionic structures. Clearly, the need for improved palliative treatments for PD continues to be a crucial goal for pharmacological discovery. Of particular importance in this regard is exploration of the therapeutic potential of currently available drugs that selectively interact with central glutamatergic systems. Conceivably, the precise targeting of glutamatergic mechanisms in the basal ganglia could provide the safest and most effective therapy for all stages of PD. In view of the neuroprotective potential of NMDA and AMPA antagonists and metabotropic agonists, intensifying the evaluation of their palliative utility for those suffering from PD seems eminently worthwhile.

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