DOI 10.1007/s00702-004-0251-7
J Neural Transm (2005) 112: 359–391

Journal of Neural Transmission
Printed in Austria

Levodopa-induced dyskinesia in Parkinson's disease*

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Received April 30, 2004; accepted October 17, 2004
Published online December 22, 2004;

Summary. Levodopa-induced dyskinesias (LID) are abnormal involuntary movements that develop progressively with repeated dopamine replacement therapy in Parkinson's disease (PD). The pathophysiology of LID comprises many functionally-related abnormalities in neurotransmission which lead to abnormalities in the rate, pattern and synchronisation of neuronal activity within and outside the basal ganglia.

In this review, we discuss the significance of the problem of LID, options currently available for avoiding and treating LID, recent advances in understanding the mechanisms responsible for the generation of LID once it has been established. In particular the discussion relates to the mechanisms underlying LID seen while levodopa is exerting its peak anti-parkinsonian actions, as it is this component of LID that is best modelled in animals and, to date, best understood. We do not aim to discuss the mechanisms by which LID is established and evolves, often termed priming, with repeated treatment, though this is an important area that has also witnessed significant advances recently (for recent review, see Blanchet et al., 2004). Finally, we define, where possible, the rationale for multiple novel therapeutic approaches that might help resolve the problem of LID.

Keywords: Parkinson's disease, basal ganglia, NMDA, cannabinoid, opioid, serotonin, synaptic plasticity.

The significance of Parkinson's disease and levodopa-induced dyskinesia

Parkinson's disease (PD) is a progressive neurodegenerative disorder, caused by loss of mesencephalic dopaminergic neurons and is characterised by reduced ability to select and initiate voluntary movements (bradykinesia, hypokinesia), rigidity and tremor at rest (Quinn, 1997). PD is extremely common amongst those over 65, an age group that, in North America, is predicted to rise from 12% to 24% over the next 30 years. The overall prevalence of Parkinson's disease in this population is in the order of 1.5–2% and increases with age.

* Lecture, 11th IWCN Congress, September 14–16, 2003 (Campbell River, BC, Canada)

While there are some significant discrepancies in reported prevalence of PD, parkinsonism and parkinsonian signs (e.g. being much higher in Bennett et al., 1996; Louis et al., 2003), the majority of studies place prevalence of PD *per se* at approximately 1% of people 65 to 74 years of age, 3% for those 75 to 84 and 5% of those 85 and older (De Rijk et al., 1997; Kis et al., 2002; Benito-Leon et al., 2003; Bergareche et al., 2004). Differences in reported prevalence may relate to methodology of assessment rather than real differences between different populations (Sevillano et al., 2002), and highlight the difficulty of defining the PD population outside specialist centres (Schrag et al., 2002). In fact, a corollary of this is that, in the community, the disease is under-diagnosed and thus many, perhaps between 20% and 80% of cases, go undiagnosed and untreated, particularly in geographically-isolated areas (De Rijk et al., 1997; Kis et al., 2002; Schrag et al., 2002; Sevillano et al., 2002).

The primary therapeutic strategy for the treatment of PD, dopamine replacement therapy, is based on attempts to compensate for the loss of dopaminergic neurons. This is achieved by the administration of L-3,4-dihydroxyphenylalanine (L-DOPA, levodopa), the direct metabolic precursor for dopamine, or dopamine receptor agonists such as pergolide, bromocriptine, ropinirole, cabergoline or pramipexole (Oertel and Quinn, 1997). Despite the widespread availability of these agents, PD remains a major problem in contemporary neurology and psychiatry, represents a significant financial burden on society and has a serious negative impact on the lifestyle and socio-economic status of those affected. The problems and limitations of current therapies are well-demonstrated by the fact that people with parkinsonism have a lower perceived quality of life (Schrag et al., 2000), a much higher risk of hospitalisation for a range of non-neurological conditions (Guttman et al., 2004) and approximately twice the risk of death, compared to age-matched controls (Bennett et al., 1996; Guttman et al., 2001). One major factor contributing to the inadequacies of current therapies for PD is that they lead to the development of unwanted, debilitating, involuntary movements ''levodopa-induced dyskinesia'' (LID).

Initially, dopamine replacement therapy dramatically improves the motor symptoms and quality of life of patients with PD. However, within a few years, treatment with levodopa induces the genesis of unwanted, debilitating, involuntary movements known as ''levodopa-induced dyskinesia'' (LID). This LID, characterised by idiosyncratic mixtures of dystonia and chorea, becomes progressively more severe with increasing duration of treatment. LID can show several patterns of expression, being most severe at peak anti-parkinsonian effect of levodopa, at the beginning and end of dose or when off-treatment (Quinn, 1998). LID can affect 45–85% of patients of PD patients within a movement disorder clinic setting (Friedman, 1985; Quinn et al., 1987; Wagner et al., 1996; Rascol et al., 2000). In a community setting, it is suggested that the approximately 30% of patients who have received a levodopa preparation, at any time, exhibit LID (Schrag and Quinn, 2000). The development, or priming, of LID over time is a complex process and is dependent on the interaction of many factors, including age of onset, disease severity, duration of therapy, treatment regimen (Friedman, 1985; Wagner et al., 1996; Schrag and Quinn, 2000). However, once the brain is primed to elicit dyskinesia it is difficult to

treat the underlying symptoms without the expression of dyskinesia. It also extremely difficult to reverse, deprime, the priming process. In fact, LID can become so severely disabling as to negate any clinical benefit from dopaminergic therapy and significant efforts must be made and costs incurred to maintain control of symptoms in the advanced PD patient. The direct annual cost of treating PD is estimated as being US$ 11 billion worldwide. In addition to the financial costs, the human burden is immense and affects not only the person with PD but a wide network of carers in many ways upon which a financial value cannot be placed. An enhanced understanding of the mechanisms responsible for dyskinesia could thus have great impact.

Current approaches to LID

Several approaches to the treatment of LID are now available though none are optimal or applicable to all patients (Ferreira and Rascol, 2000).

Five dopamine receptors are described (D1–D5), these can be grouped, on the basis of molecular biology, pharmacology and signal transduction, into two classes, D1-like (D1 and D5) and D2-like (D2, D3 and D4). *De novo* administration of D2-like dopamine receptor agonists has less propensity to prime for dyskinesia than levodopa in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned non-human primates (Bedard et al., 1986; Pearce et al., 1998; Maratos et al., 2001; Smith et al., 2002) and in man (Rascol et al., 1979, 2000; Montastruc et al., 1989; Parkinson Study Group, 2000; Lees et al., 2001). However, the anti-parkinsonian benefit of dopamine agonist monotherapy is generally not maintained with time and ''rescue'' with levodopa is required (Rascol et al., 2000; Lees et al., 2001). While levodopa/agonist combination therapy can be associated with good anti-parkinsonian control, the addition of levodopa brings with it the almost inevitable prospect of LID. There have been some indications that the use of high dose dopamine agonist therapy might be capable of depriming for dyskinesia, thus, use of an apomorphine or lisuride infusion or high dose pergolide treatment might lead to reduced ability of dopamine replacement therapy to elicit dyskinesia (Facca and Sanchez-Ramos, 1996; Manson et al., 2002; Stocchi et al., 2002). However, such approaches have not been widely employed and are likely to be associated with significant practical problems and poorly-tolerated by many patients. Thus, the increasing use of dopamine agonists, while helpful early in the disease in previously untreated patients, does not remove LID as a major problem in the management of PD.

Recently, the concept of using pharmacological adjuncts to levodopa to reduce the expression of established LID has been demonstrated by the use of the NMDA antagonist amantadine, firstly in the MPTP-lesioned non-human primate (Blanchet et al., 1998) and latterly, in the clinic (Verhagen-Metman et al., 1998c; Metman et al., 1999; Luginger et al., 2000; Del-Dotto et al., 2001). Although amantadine can be helpful in reducing dyskinesia, it may not be well-tolerated or efficacious in all patients, insufficient data are available (Crosby et al., 2003). Furthermore, amantadine has potential to reduce motor learning in healthy volunteers (Tahar et al., 2004) and its actions in reducing

LID show tachyphylaxis (Thomas et al., 2004). These limitations of amantadine may result from its mechanism of action as an NMDA antagonist. Firstly, weak or variable efficacy may result from it being only a weak blocker of channel activation (Porter and Greenamyre, 1995), its affinity and binding kinetics result in only brief blockade, in comparison to other NMDA channel blockers (Blanpied et al., 1997). Secondly, amantadine shows little selectivity for subtypes of NMDA receptors and, thus, may have extensive actions, in many brain structures, that limit its tolerability and/or efficacy (Blanpied et al., 1997). Thirdly, chronic administration of NMDA channel blocking drugs causes dysregulation of synthesis of NMDA receptor subunits, which could contribute to tachyphylaxis (Oh et al., 2001).

Similarly, surgical approaches to LID have been proposed and applied (Gross et al., 1999). Thus, in patients with previously-established LID, manipulation of the internal segment of the globus pallidus (GPi) by either deep brain stimulation (DBS) (Gross et al., 1997; Benabid et al., 1998; Kumar et al., 1998a; Burchiel et al., 1999) or by lesion (Lozano et al., 1995; Baron et al., 1996, 2000; Lang et al., 1997a; Samuel et al., 1998; Schrag et al., 1999; Fine et al., 2000; Lozano and Lang, 2001; Vitek et al., 2003) may reduce the propensity of levodopa to elicit dyskinesia, without reducing its ability to alleviate parkinsonian symptoms. Alternatively, surgery focussed on the subthalamic nucleus, either DBS (Benabid et al., 1994, 1998; Krack et al., 1997, 1998, 2003; Kumar et al., 1998a, b; Burchiel et al., 1999; Fraix et al., 2000; Molinuevo et al., 2000; Kleiner-Fisman et al., 2003; Varma et al., 2003) or lesion (Patel et al., 2003), can reduce the problem of LID by allowing the maintenance of good anti-parkinsonian benefit while reducing the required dosage of levodopa. Furthermore, it has been suggested that STN-DBS can deprime the dyskinetic brain so that it is less susceptible to elicit dyskinesia when challenged with a give dose of levodopa (Bejjani et al., 2000; Varma et al., 2003). Surgical manipulations such as these can undoubtedly reduce the problem of LID in some patients and overall probably improve the quality of life of people with Parkinson's disease (Gray et al., 2002; Romito et al., 2003). However, surgery has limitations in that, it is not applicable to all patients, it can lead to changes in non-motor function and it cannot be applied widely as there are a relatively small number of specialised centres that can provide service to all patients for whom LID is a problem (Lang et al., 1997b; Jahanshahi et al., 2000; Saint-Cyr et al., 2000; Trepanier et al., 2000; Berney et al., 2002; Doshi et al., 2002; Tamma et al., 2003). On the other hand, surgical transplants of fetal mesencephalic tissue do not remove the problem of LID, indeed it now appears that such surgery may exacerbate the problem, in some cases leading to the appearance of ''runaway'' dyskinesia present when the patient is receiving no pharmacological treatment whatsoever (Hagell et al., 2002).

An increased understanding of the mechanisms responsible for LID could highlight novel approaches to the treatment of LID. The remainder of this review focuses on how significant advances in understanding the neural mechanisms by which LID is elicited, once it has become established, have raised the possibility of more effective therapies based upon targeting not only

dopaminergic but also non-dopaminergic components of the basal ganglia circuitry (Chase, 1998; Brotchie, 1999; Metman et al., 2000; Rascol, 2000; Bezard et al., 2001; Hadj-Tahar et al., 2003).

The pathophysiology of established LID

The striatum influences the output regions of the basal ganglia, the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr), the output regions of the basal ganglia, by either a ''direct'' monosynaptic connection or an ''indirect'' network involving the external pallidal segment (GPe) and the subthalamic nucleus. The direct and indirect pathways provide means by which the striatum can have opposing actions on the activity of GPi/SNr (Kolomiets et al., 2003). Physiologically, the interplay of these processes is responsible for selection of appropriate movements and the suppression of inappropriate movements (Hikosaka, 1989; Chevalier and Deniau, 1990). Pathophysiological imbalances in the activities of the direct and indirect striatal output pathways lead to abnormal basal ganglia output, reflected in gross changes in firing rate, as well as changes in patterning and synchronisation of neuronal firing, (this basic concept has been reviewed extensively elsewhere, Penney and Young, 1983, 1986; Alexander et al., 1990; Crossman, 1990, 2000; Obeso et al., 2000b; Wichmann and DeLong, 2003). In the case of the generation of the inappropriate movements, such as LID, the net outflow from the basal ganglia is thought to be reduced.

Although, controversy remains (e.g. Obeso et al., 2000a), and a complete understanding of LID will undoubtedly require additional and alternative concepts to be incorporated, the following changes in neural function are key contributors to the mechanisms of LID.

1) Once the parkinsonian brain has been primed to elicit dyskinesia, there are significant alterations in the influence of the glutamatergic inputs to neurons of the striatum that influence other regions of the basal ganglia (Chase et al., 1998; Calon et al., 2000; Oh and Chase, 2002).
2) Abnormal glutamatergic transmission in LID, results not only in changes in the general excitability of striatal neurons but also in abnormalities in synaptic plasticity in corticostriatal synapses and abnormalities in the pattern of activity of those striatal outputs.
3) The principal abnormality is that glutamatergic drive to striatal output neurons projecting to GPi is enhanced, i.e., the direct pathway is overstimulated.
4) As the direct pathway employs GABA as its primary transmitter, there is enhanced inhibition of GPi and SNr by the direct pathway so rendering basal ganglia outputs underactive. This drives the expression of inappropriate movements.

In themselves, we propose, that these changes may be sufficient to generate dyskinesia. However, additional mechanisms are likely play a role, for instance GABAergic inhibition of GPe by the indirect pathway may be reduced, thus

making GPe overactive. This would further lead to enhanced inhibition of GPi and SNr. Thus,

1) enhanced activity in the GABAergic projections from GPe to GPi/SNr, and,
2) increased activity of the inhibitory GPe-subthalamic nucleus connection, which would lead to subsequent underactivity of excitatory subthalamic efferents to GPi and SNr, would both cause underactivity of basal ganglia outputs.

The above explanation of the mechanisms underlying LID has been extremely useful in providing a theoretical framework upon which to hang a vast amount of data and thus enable the generation of testable hypotheses. However, it must be appreciated that the concept that basal ganglia outputs, from GPi and SNr, are simply underactive in LID is far from being the full story. Indeed, the somewhat paradoxical success, in reducing LID, of an approach that further reduces GPi activity, pallidotomy, illustrates the failure of the model to encapsulate all available data well. To move beyond this simplistic viewpoint towards a more complete understanding it will be necessary to re-evaluate data and take more sophisticated approaches to studying LID. Such would recognise that, in LID, it is not simply the total neuronal activity, but also the pattern and synchronisation of firing that defines the operation of the basal ganglia circuit (Matsumura et al., 1995; Vitek and Giroux, 2000; Brown, 2003). Thus in experimental dyskinesia, within either GPi or GPe, the firing frequency in neighbouring neurons can be either increased or decreased (Matsumara et al., 1995). It now appears that the pattern of firing of individual neurons in GPe and GPi, rather than frequency alone, is abnormal following the appearance of LID in the MPTP-lesioned primate (Boraud et al., 2001). That the pattern of GPi activity, and not just reduced frequency, is responsible for the generation of LID is supported by the fact that manipulations which disrupt that pattern e.g. GPi DBS, alleviate LID, as discussed above. In addition to the pattern of firing of individual neurons, it is likely that synchronisation and correlation of firing of multiple neurons within and between regions plays an important role in the expression of LID. The basal ganglia circuitry may support several states of neuronal activity, e.g. bursting, synchronisation, oscillation, and switches between such states may represent the neuronal basis for many functions of the basal ganglia and also disease sates (Wichmann and DeLong, 1999; Brown, 2003; Ruskin et al., 2003; Williams et al., 2003; Hamani et al., 2004). Such behaviour may be an emergent property of the molecular and cellular architecture of the basal ganglia circuitry, this has been elegantly demonstrated for GPe and the subthalamic nucleus (Bevan et al., 2002 a, b; Terman et al., 2002). As an example, cross-correlation analysis of simultaneously, recorded monkey pallidal cells shows a very low level of correlated activity in the normal state. However, the induction of parkinsonism results in both increased synchronization and the appearance of oscillatory activity in the pallidum (Nini et al., 1995; Wichmann et al., 1999; Raz et al., 2000, 2001). Dopamine replacement therapy restores the normal correlation level at the pallidum in the MPTP-treated parkinsonian monkeys (Heimer et al., 2002). Unfortunately, to date, no details of the nature of correlated or oscillatory firing activity in the basal ganglia in

animals with defined LID have been reported. However, the advent of a novel drug, levetiracetam, that can alter neuronal synchronisation suggest that such studies could prove extremely interesting. Levetiracetam is a novel, and well-tolerated anti-convulsant, and exhibits unique properties that interfere with neuronal synchronisation, these contrast to other anti-epileptic drugs. Administration of levetiracetam, reduces the expression of established LID in MPTP-treated non-human primates, without affecting the anti-parkinsonian action of levodopa (Hill et al., 2003; Bezard et al., 2004). Furthermore, levetiracetam has synergistic actions with amantadine with respect to its anti-dyskinetic actions (Hill et al., 2004). If these actions of levetiracetam can be demonstrated to reflect an action due to altering neuronal synchronisation then they will represent a paradigm shift in the pharmacological treatment of LID, which has, hitherto, focussed on modulating signalling at individual neurotransmitter receptors or their downstream signalling cascades.

The pharmacology of established LID

Many factors are likely to contribute to the production of abnormal frequency, firing patterns and neuronal synchronisation in LID. These have been demonstrated to different degrees of rigour, though all have some supportive data. The remainder of this review will discuss the contribution played by multiple transmitter systems to the generation of LID once it has been established.

Role of different classes of dopamine receptors

As discussed above, dopamine D2-like receptor agonists produce less dyskinesia than LEVODOPA if given to previously-untreated patients, as described above the mechanism of priming are not he subject of this review and are discussed elsewhere (e.g. Blanchet et al., 2004). On the other hand, the role of different subtypes of dopamine receptors in eliciting LID, once it has been established, is also of great interest and might offer opportunities for therapeutic intervention in the vast majority of patients who have been previously primed with levodopa. However, if patients, or monkeys, in whom LID has been previously established, are administered dopamine D2 receptor agonist therapy, even as monotherapy, dyskinesia is evoked in a similar way to levodopa (Gomez-Mancilla and Bedard, 1991; Blanchet et al., 1993, 1997; Pearce et al., 1995; Marsden, 1998; Clarke et al., 2000; Rascol, 2000; Clarke and Deane, 2001). Similarly, in parkinsonian monkeys and patients, previously primed with levodopa to elicit LID, acute administration of D1 dopamine receptor agonists also elicit dyskinesia, though this may have different phenomenology (Pearce et al., 1995, 1999; Grondin et al., 1997; Rascol et al., 1999, 2001b). However, initial claims, in non human primate, that D1 receptor stimulation might be associated with less severe dyskinesia than LID (Grondin et al., 1997), for equivalent anti-parkinsonian doses, have not been substantiated by subsequent studies in man (Rascol et al., 2001b). The reason for this is not clear but may reflect the variability, between species or between human disease state and animal model, in basal levels of endogenous dopamine as the actions of D1-like agonists require concomitant stimulation of D2-like

receptors (Gnanalingham et al., 1995; Grondin et al., 1999; Treseder et al., 2000a, b). Thus, the expression of LID cannot be simply described on the basis of involving either D1-like or D2 like, nor once established can it be avoided by employing D1-like or D2-like agonists to alleviate parkinsonism. This does not necessarily mean that specific subtypes of dopamine receptor are not involved in eliciting LID, just that receptors of both classes are able to be involved in its production.

The study of specific dopamine receptors has been hampered by the availability of pharmacological tools selective between members of the D1-like and D2-like families. However, a body of data has emerged that make credible the concept that the D3 receptor may have a role to play in the generation of LID. Thus, in the 6-hydroxydopamine (6OHDA)-lesioned rat (which shows motor complications in many ways equivalent to LID) and in MPTP-lesioned primate models of LID, there are reports of increased, above normal, levels of D3 receptor and its mRNA (Bordet et al., 1997; Bezard et al., 2003; Guillin et al., 2003). However, these conclusions are not universally drawn, with striatal D3 levels being reduced or normal in monkeys with LID (Hurley et al., 1996b; Morissette et al., 1998) or in PD patients *post mortem*, after many years levodopa treatment and in many cases LID (Hurley et al., 1996a). This notwithstanding, in the rat, elevated D3 expression after repeated levodopa treatment of the 6OHDA rat, is confined to the direct pathway (Bordet et al., 2000), overactivity of which is a key mechanism in the pathophysiology of LID and anti-sense knockdown of striatal D3 receptor expression reduces established levodopa-induced motor complications in the 6OHDA-lesioned rat, suggesting a causative role in the production of LID (van Kampen and Stoessl, 2003). More recently it has been reported that a partial D3 agonist, BP897, can act to reduce the expression of LID in the MPTP-lesioned primate (Bezard et al., 2003; Guillin et al., 2003). As dopamine formed from levodopa is essentially a full D3 agonist it can thus be claimed that these actions result from an attenuation of D3 transmission. However, further studies are merited as full D3 antagonists are not able to reduce LID without compromising the anti-parkinsonian action of levodopa (Bezard et al., 2003; Silverdale et al., 2004), indeed it has recently been suggested that BP897 only reduces LID at the expense of anti-parkinsonian benefit (Hsu et al., 2004). Preliminary claims have been made that, in addition to its D3 properties, BP897 also interacts with a range of monaminergic receptors (Cussac et al., 2000). Given the discussion below, such interactions could underlie the albeit impressive actions of BP897 in reducing LID. If the concept of attenuation of D3 signalling as an approach to LID is sustained by further studies it highlights the possibility of developing selective D2 agonists, with little D3 activity, as a treatment for PD that will potentially allow alleviation of parkinsonian symptoms without dyskinesia, even in previously-primed patients.

An intriguing possibility is that LID may represent the stimulation of non-synaptic dopamine receptors. The priming process might reflect abnormal trafficking of dopamine receptors such that they are localised to inappropriate locations on striatal neurons and thus exert inappropriate influence of the integration of incoming information to that neuron. The administration of levodopa

or dopamine receptor agonists would stimulate dopamine receptors regardless of their precise localisation. However, if synaptic receptors were selectively targeted we have speculated that it might be possible to alleviate parkinsonism without eliciting dyskinesia even in patients that had previously been primed to elicit dyskinesia with levodopa. To date this concept is purely speculative. In fact, a single dose of LEVODOPA can alter the subcellular distribution of striatal D1 receptors, in a way that is not seen with agents with less propensity to prime for dyskinesia (Muriel et al., 1999, 2002). However, a detailed analysis of the cellular localisation of dopamine receptors in LID has yet to be performed. One means to assess the effects of selectively stimulating synaptic dopamine receptors might be to enhance the actions of endogenous, synaptically-released dopamine. Indeed, inhibition of the re-uptake of endogenous dopamine can alleviate parkinsonian symptoms without eliciting dyskinesia in primed MPTP primates (Hansard et al., 2002a, b; Pearce et al., 2002). As such effects are dependent on the presence of a pool of residual endogenous dopamine they may only be therapeutically relevant in the early stages of the disease, and thus not useful in all patients, they do however, highlight the fact that in eliciting dyskinesia the brain responds differently depending upon the source of its dopamine receptor stimulation. This suggests the involvement of different populations of dopamine receptors in mediating anti-parkinsonian actions and eliciting LID.

Table 1. Involvement of multiple receptor systems in levodopa-induced dyskinesia. Proposed sites and mechanisms of involvement in the expression of dyskinetic symptoms

Receptor	Site	Nature of abnormality in LID	Potential mechanism of involvement in LID
Glutamate NMDA (NR2A)	striatum	enhanced	Stimulation of activity of direct output pathway
Glutamate AMPA	striatum	enhanced	Stimulation of activity of direct output pathway
Cannabinoid CB1	striatum	reduced	Enhanced glutamate transmission
	GPe	reduced	Decreased GABA transmission
	GPi	enhanced	Enhanced GABA transmission
Dopamine D3	striatum	enhanced	Stimulation of activity of direct output pathway
Adrenergic $\alpha 2$	striatum/GPi	enhanced	Sensitises direct pathway to effects of dopamine
$5HT_{2A}$	striatum	enhanced	?
$5HT_{1A}$	striatum	reduced	?
μ opioid	GPi	enhanced	Inhibition of GPi outputs

Enhanced glutamatergic excitation of the direct pathway

Within the striatum, glutamatergic inputs, from the cerebral cortex and thalamus, can excite striatal output neurons by interactions with both ionotropic (NMDA, AMPA and kainate) and metabotropic glutamate (mGluR) receptors (Lovinger, 1991; Lovinger and Tyler, 1996; Pisani et al., 1997, 2001; Stefani et al., 1998; Chergui et al., 2000; Gubellini et al., 2003; Vergara et al., 2003). There are undoubtedly important functional interactions between these glutamate receptors and abnormalities in signalling, by all, probably contribute to the expression of LID. However, to date the most-studied and best understood contribution of enhanced glutamatergic signalling to the mechanisms of LID are those involving NMDA receptors. On an empirical level there are now a number of studies in patients with PD, in the MPTP-lesioned primate with LID and in the 6OHDA-lesioned rat model of LID where systemic administration of NMDA antagonists reduces LID, or related motor complications (Engber et al., 1994; Papa et al., 1995; Papa and Chase, 1996; Blanchet et al., 1998, 1999; Verhagen-Metman et al., 1998a, b, c; Del Dotto et al., 2001; Chassain et al., 2003). The effects appear to be mediated by blockade of NMDA transmission within the striatum (Papa et al., 1995). Such blockade of excessive striatal NMDA receptor-mediated excitation probably underlies the ability of amantadine to reduce LID in man. A more detailed understanding of this excitation is likely to lead to the development of treatments for LID that are even more effective than amantadine. Several lines of investigation may bear fruit and will be discussed below.

NMDA receptors are comprised of complexes of subunits of 2 families, NR1 and NR2. There are 8 splice variants of NR1 (NR1a–h) and 4 genes encoding NR2 subunits (NR2A–D). Subunits from each family combine, probably as tetramers, of 2 NR1 and 2 NR2 subunits, to form functional receptors (Monyer et al., 1994). Receptors with different subunit compositions have different physiological and pharmacological properties and are expressed heterogeneously in different brain region in a manner that is regulated during development, physiologically in the adult and in disease processes (Buller et al., 1994; Goebel and Poosch, 1999).

In the MPTP-lesioned primate, established LID is associated with enhanced levels of striatal NMDA receptors, particularly those containing NR2A subunits (Calon et al., 2002b). Furthermore, studies in a the 6OHDA rat model of motor complications of dopamine the replacement therapy in PD, suggest that enhanced phosphorylation of serine residues on NR1 and NR2A, but not NR2B, subunits of striatal NMDA receptors accompanies repeated, intermittent treatment of the parkinsonian brain (Oh et al., 1999; Dunah et al., 2000). This enhanced serine phosphorylation is driven by activation of calcium/calmodulin-dependent protein kinase II (CaMKII). Similarly, both NR2B and NR2A subunits of striatal NMDA receptors exhibit enhanced phosphorylation of tyrosine residues in the rat model of LID (Oh et al., 1998; Dunah et al., 2000). These processes are driven by D1 receptor activation. This is of interest as, D1 receptors preferentially modulate the activity of the direct striatal output pathway so highlighting one potential means by which NMDA signalling on the direct pathway may be abnormal and contribute to overactivity of this

connection in LID. That such abnormal phosphorylation contributes to LID is suggested by the findings that inhibition of CaMKII and tyrosine kinases reduce motor fluctuations in the rat model of LID (Oh et al., 1998, 1999). How, or why, such hyperphosphorylation might lead to LID is less clear. However, it is known that phosphorylation of NMDA receptor subunits can modulate the probability of channel opening and can affect their subcellular distribution and membrane anchoring. Of particular interest, are findings that tyrosine phosphorylation of NR2A and NR2B leads to rapid trafficking of NMDA receptors, from the cytoplasm, to the synapse and has a requirement for D1 receptor activation (Dunah and Standaert, 2001; Dunah et al., 2004). Such a mechanism is an attractive candidate for the molecular basis of enhanced NMDA receptor-mediated excitation of the direct pathway in LID. Given the diversity of cellular functions they regulate, it unlikely that the direct targeting of the kinases and phosphatases controlling NMDA phosphorylation is likely to lead to useful therapeutics for LID. However an understanding of which of the many abnormal phosphorylation events are responsible for LID and the mechanisms by which abnormal kinase and phosphatase activity occur does have the potential for defining novel therapeutic strategies. For instance, it is likely that targeting NMDA receptors with specific subunit compositions could form the basis of a treatment with better efficacy and tolerability than amantadine. To this end it has already been suggested that hyperphosphorylation of NR2B subunits is critical to LID and that targeting of these receptors selectivity may be associated with good anti-dyskinetic actions (Oh et al., 1998; Blanchet et al., 1999) while blockade of NR2A-containing NMDA receptors may exacerbate LID (Blanchet et al., 1999).

In addition to NMDA transmission, signaling at non-NMDA classes of glutamate receptors may contribute to LID. In fact, there is increasing evidence to support a role for enhanced striatal AMPA receptor signaling in the production of LID. While the total levels of AMPA receptors are either normal (Silverdale et al., 2002) or only moderately increased (Calon et al., 2002b) in the MPTP-lesioned primate with LID, the development of LID may be associated with an increased phosphorylation of the GluR1 subunit of AMPA receptors (Oh et al., 2003). Additionally, blockade of AMPA receptors, but not NMDA receptors, can reverse some of the changes in strital gene expression that are thought to be involved in LID (Perier et al., 2002). That these changes contribute to the production of LID is suggested by findings that AMPA antagonists have anti-dyskinetic actions if administered as adjunctive therapy with levodopa in the MPTP-lesioned primate (Konitsiotis et al., 2000). Furthermore, we have recently shown that the anti-convulsant topiramate, which inhibits AMPA receptor subunit phosphorylation (Gibbs et al., 2000; Angehagen et al., 2004; Poulsen et al., 2004), can reduce the expression of established LID in the MPTP-lesioned primate (Silverdale et al., in press).

Abnormal synaptic plasticity at corticostriatal synapses

The alterations in striatal glutamatergic transmission highlighted above raise the possibility that abnormal learning processes and/or synaptic plasticity may

be a component of the mechanisms of LID. Glutamate transmission in the striatum, as elsewhere in the brain, is critical for learning processes and is capable of exhibiting several forms of plasticity. Thus, when studied at the cellular level, in the normal striatum, high frequency stimulation (HFS) of striatal afferents can lead to a maintained enhancement of the strength of synaptic transmission at corticostriatal synapses, the well-described phenomenon of long-term potentiation (LTP) (Artola and Singer, 1993; Charpier et al., 1999; Spencer and Murphy, 2000, 2002; Picconi et al., 2003). With different experimental protocols, where interneurons as well as afferents are stimulated, HFS can induce a maintained decrease in the efficacy of corticostriatal synaptic transmission, long-term depression (LTD) (Calabresi et al., 1992; Spencer and Murphy, 2000; Gerdeman et al., 2002). On the system level, it is also clear that the striatum participates in procedural or habit learning, which is distinguished from the episodic, or explicit, memory system based in the hippocampal formation (Graybiel, 1995, 1998). The dopamine containing neurons of the midbrain are thought to provide a ''reward'' signal to the striatum and provide a reinforcement signal for the learning of associations between different sensorimotor signals and may be responsible for adapting expectations and behaviours to novel or changing environments (Aosaki et al., 1994; Waelti et al., 2001; Schultz, 2002; Schultz et al., 2003). As LID bears many hallmarks of abnormal motor learning and has properties reminiscent of forms of synaptic plasticity, the concept that it represents, or at least involves, abnormal motor learning/plasticity is attractive, on an intuitive level at least, and has, in its broadest sense, been previously proposed (Calabresi et al., 2000a; Calon et al., 2000; Graybiel et al., 2000; Lovinger et al., 2003).

Until recently the lack of studies on learning or plasticity in animal models of LID had left this proposal as purely speculative. However, recent studies have identified abnormalities in synaptic plasticity that may accompany LID (Picconi et al., 2003). Thus, the ability to induce striatal LTP is abolished following dopamine depletion but reinstated following long-term LEVODOPA therapy. However, when such therapy is associated with the development of abnormal involuntary movements, that are likely to be a rodent correlate of LID, a remarkable difference in this plasticity is observed. In the normal state, established LTP can be reversed, depotentiated, by low frequency stimulation. In LID, this bi-directional plasticity is lost and, thus, synapses become 'trapped' in an LTP state. The mechanisms underlying this appear to reflect enhanced Thr43 phosphorylation of DARPP-32 and inhibition of protein phosphatase 1 (PP1). These processes are associated with D1 receptor signalling, a characteristic that may explain the relative overactivity of the direct, over indirect, striatal output pathways in LID.

In understanding the relationship between LID and abnormal synaptic plasticity, such as described by Picconi et al., a major challenge is to understand the contribution of that abnormal synaptic plasticity to the different components of LID, i.e. the priming process, the production of LID once priming is established and the maintenance of the brain in the primed state. The experimental paradigm they employed makes it likely in this case that the inability to depotentiate LTP is associated with the processes responsible for eliciting LID, once priming

has been established and not the priming process. It is also important to appreciate whether abnormalities in synaptic plasticity that are described as occurring in animal models of LID represent mechanisms underlying the production of LID, responses to the production of LID or are in fact problems that arise because of a disruption of a cellular process that is common to both LID and that particular form of synaptic plasticity. In the light of the work described above one might consider that strategies aimed at restoring the bi-directional plasticity, and reverse trapped LTP, may be a potential avenue for therapy of reducing the expression of established LID, and not the priming process. However, when removed from the animal with established LID, striatal neurons are not already trapped in LTP, but only become so during the artificial conditions of the experimental procedure that induces LTP. Thus it seems unlikely that being trapped in LTP is actually the mechanism responsible for LID. Rather, this phenomenon, is more likely to be caused by a process that is abnormal and also responsible for LID, e.g. Thr43 phosphorylation of DARPP-32 or PP1 inhibition which also disrupts the LTP process. This latter concept, invoking the involvement of proteins, the function of which are, at present, difficult to manipulate via pharmacological means, highlights the potential value of employing research strategies based on knockout mice. Such strategies have been powerfully employed to define the physiological role of DARPP-32 in a variety of contexts (Fienberg et al., 1998; Hiroi et al., 1999; Calabresi et al., 2000b; Fienberg and Greengard, 2000; Svenningsson et al., 2000) and could be extended to the understanding of LID following the recent validation of a mouse model of LID (Lundblad et al., 2004).

Although, our understanding of these issues is still evolving, correction of the molecular abnormality responsible for eliciting LID, once it has been established, would also be expected to re-establish the ability to depotentiate established LTD. The reverse may also be true to some extent, re-establishing the ability to depotentiate may suppress the expression of LID. The mechanisms of depotentiation of striatal LTP depotentiation are thus of potential interest with respect to LID. An alternative approach to preventing synapses becoming trapped in LTP, and thus also, perhaps, attenuating the expression of LID, might be to interfere with processes responsible for establishing LTP. In this respect, it is of interest that LTP induction has recently been described as involving NR2A-, rather than NR2B, containing NMDA receptors (Liu et al., 2004; Massey et al., 2004), a phenomenon that is consistent with our suggestion, above, that NR2A-containing NMDA receptors may be involved in the expression of LID.

LTP and LTD at corticostriatal synapses involves enhanced and decreased, respectively, transmission at AMPA receptor mediated synapses. AMPA receptors are heteromeric complexes comprising different combinations of the subunits GluR1–4. The detailed molecular mechanisms of striatal LTP and LTD remain to be elucidated, however, in the CA1 region of the hippocampus much progress has been made. LTP is driven by the redistribution of GluR1 and GluR2-containing AMPA receptors to the synaptic membrane (Shi et al., 2001). Trafficking of GluR1/2 receptors to the synapse during LTP is dependent on phosphorylation of GluR1 and interactions between GluR1 and the

synapse associated proteins (SAPs) PSD95 and SAP97 (Hayashi et al., 2000; Piccini and Malinow, 2002). Depotentiation results from a reversal of these processes e.g. PP1-mediated dephosphorylation of GluR1 (Huang et al., 2001). Thus, we propose that in LID, inhibition of PP1 activity (Picconi et al., 2003) would trap GluR1/2 AMPA receptors at the synapse. One means to restore striatal depotentiation would thus be to reverse the Thr43 phopsphorylation of DARPP-32 and the associated inhibition of PP-1. This approach though attractive from a molecular perspective is unlikely to represent a viable therapeutic approach given the ubiquity of the kinases and phosphatases involved. Alternatively, other mechanisms responsible for depotentiating LTP, e.g. activation of mGluRs (Bashir and Collingridge, 1994) might be more ''druggable''. More options for treating LID might be identified by considering the processes underlying LTD. Although there are likely some mechanistic similarities, the mechanisms of striatal LTD are distinct from depotentiation. LTD is dependent on removal, from the synapse, of AMPA receptors containing GluR2 and GluR3 subunits. Their removal is dependent upon interactions between GluR2 and SAPs (Daw et al., 2000; Kim et al., 2001) and ultimately by endocytosis (Luscher et al., 1999). We hypothesise that the GluR2 subunit of GluR1/2 AMPA receptors trapped in LTP could be made to act as bait for the mechanisms responsible for internalising GluR2/3 receptors in LTD. By initiating an internalisation process targeting GluR2/3 subunits, GluR1/2 receptors will also be internalised, LTP depotentiated and might be LID reversed.

In support of this latter contention, stimulation of cannabinoid CB1 receptors is an integral part of the mechanisms underlying LTD in the striatum (Gerdeman et al., 2002) and stimulation of CB1 receptors reduces LID in both the MPTP-lesioned primate (Fox et al., 2002) and PD patients (Sieradzan et al., 2001). Several other components of the mechanisms responsible for inducing LTD have been described either within the striatum and elsewhere (Centonze et al., 2003; Lovinger et al., 2003). Thus, within the striatum, in addition to requiring CB1 stimulation, LTD is enhanced by, or dependent upon, stimulation of mGluRs (Sung et al., 2001), nicotinic acetylcholine receptors (Partridge et al., 2002), administration of lithium (Calabresi et al., 1993), activation of nitric oxide synthase and enhancement of cGMP levels (Calabresi et al., 1999). These and related approaches might also be considered as having potential to form the basis of treatments that would suppress the production of established LID.

Abnormal modulation, by non-dopaminergic mechanisms, of glutamate, GABA and dopaminergic signalling throughout the basal ganglia circuitry

A key feature of the functional organisation of the basal ganglia is that signalling by the principal excitatory and inhibitory transmitters of the circuit, glutamate, GABA and dopamine, are modulated by a vast array of diverse mechanisms. Although there are clearly abnormalities in signalling by the principal transmitters, these may not necessarily be the primary, or at least only, abnormality of cell–cell communication responsible for LID. Thus changes in these modulatory mechanisms may contribute to aberrant communication in

LID, reversal of these might represent a novel therapeutic approach. Alternatively, attempts by modulatory mechanisms to compensate for abnormalities in glutamate, GABA and dopamine signalling induced by repeated dopamine replacement therapy may be insufficient to suppress LID. However, enhancement of such compensatory mechanisms may attenuate the expression of LID. As will be discussed below several such opportunities for developing novel therapeutics to reduce established LID have been described over the last decade. In some cases the exact mechanism of action is unclear but an emerging understanding of the pharmacology is a common feature and many drugs are now progressing towards, or already in, clinical trial.

Cannabinoids

An important system modulating classical transmission in the basal ganglia is the cannabinoid CB1 receptor system. CB1 receptors are richly represented in both the target regions of the direct and indirect pathways as well as in the striatum and play crucial roles in regulating basal ganglia function at the behavioural level (Maneuf et al., 1997; Sanudo-Pena and Walker, 1997; Sanudo-Pen et al., 1999; Di Marzo et al., 2000; Segovia et al., 2003). These behavioural effects reflect a diversity of cellular actions. Activation of CB1 blocks the release and uptake of striatal glutamate (Gerdeman and Lovinger, 2001; Brown et al., 2003). Such effects might contribute to the role of endogenous cannabinoids in LTD (Gerdeman et al., 2002), described above. Furthermore, cannabinoids regulate GABAergic signaling in GPe and the output regions of the basal ganglia, by blocking the uptake and release of GABA (Maneuf et al., 1996a, b; Szabo et al., 1998; Wallmichrath and Szabo, 2002). The CB1 system is also notable in that it regulates, and is regulated by, other transmitter systems critical to LID. Thus, the synthesis of one of the endogenous ligands of CB1, anandamide, is under positive control of D2 receptors (Giuffrida et al., 1999) while another, 2-arachidonyl-glycerol is suppressed by D2 activation (Di Marzo et al., 2000). There is also evidence for interactions with opioid system (e.g. cross-desensitization, decreased opioid peptide levels in CB1 knock-out mice) (Manzanares et al., 1998; Navarro et al., 1998; Vigano et al., 2003), D2 receptors at the level of G-protein coupling (Jarrahian et al., 2004) and $5HT_{1B}$ receptors (Hermann et al., 2002). Given the diversity of actions and the number of regions throughout the basal ganglia in which endogenous cannabinoids could potentially contribute to the expression of LID, it is perhaps not surprising that although several valuable sets of data relating to receptor levels and signal transduction have been obtained in animal models of LID (Zeng et al., 1999; Lastres-Becker et al., 2001) and in PD patients post mortem (Lastres-Becker et al., 2001; Hurley et al., 2003), the full extent of their role in LID remains to be defined. In fact, it has been suggested that, due to actions in different regions either CB1 agonists or antagonists could have beneficial effects in reducing established LID (Lastres-Becker et al., 2001; Brotchie, 2003). To date, the CB1 receptor agonist, nabilone, has been shown to have positive effects in reducing established LID in a clinical trial (Sieradzan et al., 2001), while both agonists and antagonists were shown to improve the

symptoms of LID in animal models of LID (Fox et al., 2002; Segovia et al., 2003; Fox et al., in press).

Monoamines

In addition to dopamine, two other monoamines, noradrenaline and 5-hydroxydopamine (5-HT), are likely to play a role in basal ganglia function and in LID. For instance, the alpha$_2$ adrenergic system modulates the sensitivity of the direct pathway (Hill and Brotchie, 1999b). Activation of alpha$_2$ receptors may be crucial for setting the balance between the direct and indirect pathway and making it difficult to treat PD, in the primed state, without eliciting LID. Once LID has been established, alpha$_2$ antagonists have the ability to attenuate its production following subsequent levodopa challenges in rat (Henry et al., 1998; Lundblad et al., 2002), non-human primates (Gomez-Mancilla and Bedard, 1993; Henry et al., 1999b; Grondin et al., 2000; Fox et al., 2001; Savola et al., 2003) and in PD patients (Rascol et al., 2001a). This ability of alpha$_2$ antagonists to allow the alleviation of parkinsonism without producing LID appears to relate to the fact that alpha$_2$ antagonism reduces the sensitivity of the system to produce LID. Thus in the absence of alpha antagonism, levodopa elicits its anti-parkinsonian and pro-dyskinetic actions at similar doses, alpha$_2$ receptor blockade shifts the dose response curve for producing LID to the right. Thus, in the presence of a dose of levodopa that is optimal for alleviating parkinsonian symptoms reduced LID is seen. If supra-optimal doses of levodopa are employed, the ability of alpha$_2$ antagonism to reduce LID is compromised. Although the effects of alpha$_2$ antagonists in reducing LID are robust are have been demonstrated by several compounds and several groups across species, two potential limitations of the approach must be highlighted. Firstly, it appears that the actions of alpha$_2$ antagonists in reducing LID involve blockade of receptors stimulated by levodopa, or one of its metabolites, thus alpha$_2$ antagonists do not reduce dopamine agonist induced dyskinesia (Fox et al., 2001). Secondly, it may be necessary to consider the issue of tolerability, especially with respect to potential cardiovascular effects, if these agents are to be widely applied in LID. Thus one trial with idazoxan was plagued by unacceptably high drop out rates (Manson et al., 2000). Such problems may not apply to all alpha$_2$ antagonists.

In a similar way, 5-HT receptors are located at several sites throughout the basal ganglia and have been shown to represent potential targets for treatment for LID (see Nicholson and Brotchie, 2002 for review). Agents which act as agonists at $5HT_{1A}$ have been shown to reduce LID in the MPTP-lesioned primate and the 6OHDA rat (Bibbiani et al., 2001). Similar effects are reported for antagonists at $5HT_{2A}$ receptors (Oh et al., 2002), though these results have not been substantiated in man by the use of quetiapine (Dekeyne et al., 2003). In fact, multiple classes of 5HT receptors probably contribute to LID and drugs with multiple actions may prove useful. In this respect, the observations that MDMA (''Ecstasy'', which non-selectively enhances several aspects of 5HT transmission) reduces LID are of great interest (Iravani et al., 2003). Furthermore, fluoxetine (which reduces 5HT re-uptake) attenuates apomorphine-induced dyskinesia in man (Durif et al., 1995). Identification of the precise

combination of 5HT receptors involved in these effects, and the discovery of drugs that can target them, offers great hope for defining novel strategies for LID.

Opioids

A role for opioid systems has been suggested in LID, though in recent years the nature of this role has become less clear, as conflicting data have emerged from different groups employing different animal model of LID. Within the basal ganglia, opioids are used as co-transmitters with GABA in both the direct and indirect striatal output pathways (Steiner and Gerfen, 1998). There are much data to support the concept that there is increased synthesis of the opioid peptide precursors, preproenkephalin A and B (PPE-A and PPE-B), in striatal output neurons in animal models in LID (Engber et al., 1991, 1992; Taylor et al., 1992; Cenci et al., 1998; Duty et al., 1998; Henry et al., 1999a, 2003; Westin et al., 2001; Winkler et al., 2002) and in PD patients, *post mortem* (De Ceballos et al., 1993; Calon et al., 2002a; Henry et al., 2003). The aforementioned changes do not develop following long-term *de novo* use of dopaminergic agents that are less likely to cause dyskinesia, e.g. bromocriptine, lisuride or ropinirole (Henry et al., 1999a; Tel et al., 2002; Ravenscroft et al., 2004). Moreover, PET studies demonstrate enhanced opioid transmission in the basal ganglia of patients with LID (Piccini et al., 1997). Thus, that there is an association between enhanced opioids and LID is well-accepted. However, a controversy arises as to whether this relates to the mechanisms responsible for the expression of established LID, the priming process and/or the maintenance of the primed state, and whether they contribute to, or result from, these processes. Efforts to address this issue have been confounded by the fact that there are probably differences between species with respect to processing opioid peptides, there are likely complex interactions between two or more subtypes of opioid receptor and that opioids probably play roles in several processes.

The products or PPE-A and PPE-B, the enkephalins, dynorphins and alpha-neoendorphin, can activate all three major classes of opioid receptor, mu, kappa and delta. All three opioid receptors regulate signalling at several sites within the basal ganglia circuitry and all of which have been suggested as showing some abnormal function in animal models of LID. Kappa opioid receptors are expressed primarily pre-synaptically on dopaminergic, glutamatergic and GABAergic nerve terminals in the striatum, GPe and GPi/SNr where they inhibit neurotransmitter release (Maneuf et al., 1995; Schoffelmeer et al., 1997; Gray et al., 1999; Hill and Brotchie, 1999a; Rawls et al., 1999; You et al., 1999; Ogura and Kita, 2000). Kappa receptors are also located post-synaptically on striatal neurons (Spadoni et al., 2004) and on GPe cell bodies (Ogura and Kita, 2000) which they hyperpolarise. Kappa receptors are substantially down-regulated in the striatum and substantia nigra in 6OHDA rats chronically treated with levodopa (Johansson et al., 2001). In the striatum, mu opioid receptors are found pre-synaptically on glutamatergic corticostriatal terminals and inhibit the release of glutamate (Herrera-Marschitz et al., 1998). In GPe, mu opioid receptors are expressed both post-synaptically, where they reduce excitability (Stefani et al., 2001) and pre-synaptically on GABAergic terminals of the

indirect pathway where their activation reduces inhibition (Stanford and Cooper, 1999). Delta opioid receptors are located on GABA terminals within GPe (Stanford and Cooper, 1999). In the striatum, delta receptors play a role in regulating glutamate and acetylcholine release, though these effects may not be direct but transynaptic involving a release of dopamine (Arenas et al., 1991; Pentney and Gratton, 1991; Rawls and McGinty, 2000). Given this diversity of effects across the nuclei of the basal ganglia, many hypotheses, which are not necessarily mutually-exclusive, have been put forward to define the role of opioids in LID or potential means to modulate opioid transmission and treat LID. In the absence of extensive site and receptor class-selective manipulations in animal models of LID the true, rather than potential role, remains unclear. In fact, even systemic studies to demonstrate a role, at some point of the circuit, for opioids in LID have produced conflicting data. That enhanced opioid transmission within the basal ganglia might contribute to the generation of LID once it has been established is suggested by the findings that subtype-selective opioid receptor antagonists can reduce established LID in rodent (kappa only) and primate (mu and delta but not kappa) models of Parkinson's disease (Newman et al., 1997; Henry et al., 2001). On the other hand, data with non-subtype-selective antagonists are less convincing with primate studies showing either no effect (Gomez-Mancilla and Bedard, 1993), attenuation (Henry et al., 2001; Klintenberg et al., 2002) or exacerbation (Samadi et al., 2003) of LID and clinical studies showing no effect (Nutt et al., 1978; Rascol et al., 1994; Manson et al., 2001; Fox et al., 2004) or reduction (Trabucchi et al., 1982) in LID by naloxone or naltrexone. It is suggested that there may be opposing roles, with respect to generating LID, for different subtypes of opioid receptor in different regions of the basal ganglia. These may have relatively different roles in different species or in different forms of LID (e.g. chorea vs. dystonia). Thus it appears likely that an opioid based therapy for LID that acts as an adjunct to levodopa to reduce established LID may have to be based on an approach that selectively targets a single class of opioid receptor.

Conclusions

Much progress has been made in understanding the mechanisms responsible for eliciting LID once it has been established. LID results a combination of factors that include alterations in signalling at many neurotransmitter receptors, abnormal synaptic plasticity and altered firing pattern and synchronicity in the basal ganglia circuit. Several novel therapeutic approaches based upon this understanding have already been anticipated and will continue can be developed. It is perhaps likely that several different classes of drug will be required as some will have efficacy in patients with dyskinesia of different forms, e.g. chorea compared to dystonia, or that some drugs will reduce LID more effectively than dopamine agonist-induced dyskinesia. An intriguing possibility is that the pendulum of biopharmaceutical opinion may swing from a position where the industry has focussed on defining novel therapeutics based on highly selective targeting of single receptors to one where they embrace the possibility of drugs that can have multiple actions. The design of drugs combining, into a single

molecule, multiple actions, each individually selective, is both a theoretical and practical challenge. That such drugs might be valuable is not only illustrated by the above discussion but also by the actions of ''old'', non-selective drugs, e.g. clozapine (dopamine/5HT) (Durif et al., 2004), mirtazapine (noradrenaline/5HT) (Pact and Giduz, 1999; Meco et al., 2003) or piribedil (dopamine/5HT/noradrenaline) (Smith et al., 2002), all of which have been suggested as having value in the control of LID.

Acknowledgements

Our research is generously supported by the Krembil Neuroscience Fund, Michael J. Fox Foundation and Parkinson's Society Canada.

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