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Imaging Dyskinesias in Parkinson's Disease

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative movement disorder characterised by the motor features of tremor, rigidity and bradykinesia. These features are associated with the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta and a subsequent deficiency in striatal DA, which is required for the effective control of movements. However, there is evidence of a more diffuse pathology in PD (Braak et al., 2004) with other, non-DA neurotransmitter systems possibly playing a role (Kish et al., 2003, 2008; Remy et al., 2005; Albin et al., 2008; Politis et al., 2010a).

To date, regular administration of the direct metabolic precursor for DA, L-3, 4-dihydroxyphenylalanine (L-DOPA) remains the most effective treatment of PD symptomatology. L-DOPA therapy is most optimally effective in the early stages of the disease and long term use leads to the appearance of motor complications such as involuntary movements, so-called L-DOPA-induced dyskinesia (LID). LID represents a debilitating complication of L-DOPA therapy in PD and is experienced by the vast majority of patients (estimates range between 40-90% between 4 and 10 years after initiation of L-DOPA therapy) (Racol et al, 2000; Ahlskog and Muenter, 2001). The mechanisms underlying LID remain obscure. It is known that LID is observed following DA therapy and that there is a time-lag between the initiation of DA therapy and the emergence of LID. Risk factors commonly associated with the development of LID include PD severity, L-DOPA dose and duration of L-DOPA therapy.

Positron emission tomography (PET) neuroimaging provides a useful tool for assessing *in vivo* functionality of basal ganglia in the PD brain. As such, the use of specific radiotracers permits insight into the integrity of both pre- and postsynaptic DA function, which could help elucidate some of the pathophysiological mechanisms underlying LID. Furthermore, over the last decade or so, PET studies have provided evidence that non-DA neurotransmitter systems may be involved in the development of LID. For example, PET has been used to investigate the role of different neuropeptides in LID, such as opioids and NK1, preliminary findings implicating the role of adenosine A_{2A} receptors and more recently promising results have emerged suggesting that the serotonergic system may possess a valuable role in the emergence of LID in PD.

Taken together, the *in vivo* findings to date have provided valuable information regarding the function of various neurotransmitter systems in the occurrence of LID and support the use of PET brain imaging to further explore these investigations. Considering the promising evidence suggesting that non-DA neurotransmitter systems may have a role in the pathogenesis of LID, further manipulation of these systems may offer an alternative

therapeutic approach in abating LID and preventing their initial development. Such investigations are vital as consequences of LID are pertinent to both the patients' quality of life and healthcare services and costs.

This chapter will review the use of PET imaging in the attempt to delineate the possible mechanisms underlying LID in PD. The imaging data available to date will be discussed supporting these mechanisms in relation to both DA and non-DA neurotransmitter systems including opioid, adenosinergic, glutamatergic and serotonergic systems.

2. LID in PD: incidence and phenomenology

LID is a common complication of L-DOPA treatment. It has been estimated to occur in approximately 40-50% of PD patients 4-6 years post-initiation of L-DOPA treatment (Ahlskog and Muentert, 2001) rising to approximately 90% after 10 years of treatment with an estimated incidence of approximately 10% per year of treatment (Rascol et al., 2000). Studies suggest that LID often initiates in the foot, ipsilateral to the side most affected by PD (Marconi et al., 1994). Somatotopically, the foot area corresponds to the dorsolateral striatum, an area which has been shown to be affected by DA denervation in the early stages of PD and is innervated by the ventrolateral portion of the substantia nigra (Fearnley et al., 1991).

The phenomenology of LID is diverse, encompassing: chorea, athetosis, dystonia, stereotypy and ballism. However, there are three many types of LID observed in PD patients in relation to their L-DOPA treatment. The most common is called 'peak-dose' LID which is characterised by both choreic and dystonic movements occurring during L-DOPA peak plasma concentration (60-90 minutes following L-DOPA administration) (Contin et al., 2000), i.e. when the L-DOPA is optimally abating PD motor symptoms. This type of LID is characterised by a sequence of Improvement-Dyskinesia-Improvement (IDI) and can often be improved by reducing the L-DOPA dose (for review see, Fahn, 2000). A less common form of LID is termed 'biphasic' dyskinesia. This form of LID follows a sequence opposite to the peak-dose form, of Dyskinesia-Improvement-Dyskinesia (DID). A further, form of LID termed 'yo-yo' dyskinesia does not follow an Improvement-Dyskinesia sequence with the involuntary movements appearing and abating at various points throughout the L-DOPA-dose cycle, therefore, it does not seem to be related to L-DOPA dosing (Nutt and Wooton, 1995). Finally, an unusual form of LID occurring when the patient is in an 'off' state, i.e. they are not taking any L-DOPA medication and is termed 'off-phase' dyskinesia. This form of LID has been observed in patients following surgical interventions, such as deep brain stimulation (DBS) and neural transplantation with fetal tissue (Freed et al., 2001; Hagell et al., 2002; Olanow et al., 2003). The off-phase dyskinesia observed following neural transplantation are named, 'graft-induced' dyskinesia (GID) and currently is not known whether they share the same pathogenic mechanisms as LID.

The initial presentation of LID is often mild with the majority of patients preferring to continue the L-DOPA therapy reaping the therapeutic benefits while experiencing some form of LID, rather than terminate L-DOPA therapy with its associated decrease in mobility (Hung et al, 2010). Fatigue and exhaustion levels increase as LIDs develop and there is increased risk of injury for the patient. LID usually appear at the point where the disease is advancing and larger L-DOPA doses are required (Thanvi et al., 2007).

Despite the increased frequency and the clinical significance, the underlying mechanisms of LID in PD are not clear. It has been suggested that the development of LID may be

dependent on several clinical risk factors including, disease severity, extent of DA denervation, and dose and duration of L-DOPA treatment. However, considerable efforts have been devoted to developing neuroimaging techniques to study the basal ganglia (the set of structures most affected by DA denervation leading to PD motor symptoms) (Eidelberg and Edwards, 2000; Feigin et al., 2001; Eidelberg, 2009). PET imaging in particular has provided a useful *in vivo* tool to assess the DA as well as other neurotransmitter systems in relation to LID in PD.

3. Animal models of LID

Two animal models commonly used to investigate LID pathogenesis are the 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine [MPTP]-lesioned primate model and 6-hydroxydopamine [6-OHDA]-lesioned rat model. MPTP is a lipophilic substance which can efficiently cross the blood-brain-barrier and subsequently inhibit complex 1 of the mitochondrial respiratory chain (Heikkilä et al., 1985) thus inducing parkinsonian, behavioural, neurochemical and pathological effects (Jenner et al., 1984). The 6-OHDA rat model utilises the 6-OHDA, a nonspecific catecholaminergic toxin. Following administration of the toxin *via* stereotaxial surgery, induction of unilateral lesions along the nigrostriatal pathway allow permanent DA depletion and observation of Parkinsonian deficits can be achieved. In both models, L-DOPA is administered to reproduce human LID (dyskinetic group) and compared to at least one control group (non-dyskinetic group) which may or may not be lesioned, but will not have LID induced.

To date, findings from these studies appear to corroborate what is observed clinically; that is, the degree of DA denervation is associated with LID development. However, interesting findings from MPTP-treated models, revealed that primates which did not develop parkinsonian motor symptoms, did go on to develop LID, indicating that the threshold of DA denervation required to induce LID is lower than that of PD symptomatology (Sassin et al., 1975). Furthermore, LID has been effectively induced in normal, unlesioned primates (Mones et al., 1973). Indeed, L-DOPA dosage in animal studies are invariably much higher than in patients studies or administered in clinic and as such may explain the swift development of LID (Di Monte et al., 2000). Nonetheless, 6-OHDA-lesioned rats have demonstrated that daily administration of L-DOPA induces LID, emerging 20-30 minutes after administration (Lundblad et al., 2002). This observation is comparable to the peak-dose dyskinesia observed in PD patients. Again in 6-OHDA-lesioned rats, L-DOPA dose was shown to modulate dyskinesia development, i.e. a therapeutic dose of L-DOPA (6-10 mg/kg L-DOPA/day) produced LID in nearly all rats within 2-3 weeks compared to a larger L-DOPA dose (50 mg/kg L-DOPA/day) which shortened latency, and increased the severity and incidence of LID induced (Lundblad et al., 2010).

Furthermore, L-DOPA leading to a priming effect has been demonstrated in both 6-OHDA-lesioned rats and MPTP-lesioned primates, with recurrence of LID appearing more readily compared to primates who did not receive any L-DOPA or were only partially lesioned (Cenci et al., 1998; Pearce et al., 1998; Andersson et al., 1999; Johansson et al., 2001; Maratos et al., 2001; Delfino et al., 2004). Moreover, primates who were lesioned, exhibited LID after a single dose of L-DOPA compared to partially lesioned primates where several doses were required before any LID developed (Di Monte et al., 2000). However, it has also been shown that the paradigm of lesion induction or pulsatility of L-DOPA treatment may play a role in LID induction (Jenner, 2003; Schneider et al., 2003). The extent of nigrostriatal DA neuronal

loss required before LID is exhibited in 6-OHDA-lesioned rats has been proposed as 80% denervation, indicating that DA denervation is not solely responsible for the induction of LID in rats, and likely not the sole contributory factor in PD patients either (Winkler et al., 2002). It is generally thought that both presynaptic (production, storage, release and reuptake of DA by dopaminergic neurons in the nigrostriatal pathway) and postsynaptic (receptor and second messenger signaling pathway status in striatal neurons) DA components are critical for the development of LID. A presynaptic mechanism proposed as a contributory factor of LID development relates to the administration of L-DOPA resulting in a dramatic increase in synaptic DA levels subsequently leading to an alteration in the degree of DA receptor stimulation (Carta et al., 2006). Clinically this pathologic mechanism corresponds to peak-dose dyskinesias (de la Fuente-Fernandez et al., 2001, 2004). It has been suggested that a decrease in the pre-synaptic 'buffering' is not dependent upon the degree of pre-synaptic denervation (Sassin et al., 1975).

Postsynaptically, LID may result from dysplastic changes occurring following the destruction of DA input to the striatum and subsequent L-DOPA administration (Hirsch et al., 2000). Alterations at the synapse level may cause a 'denervation sensitivity' and as such modifying the downstream cascade including the second messenger and signalling pathways ultimately leading to the development of dyskinesia (Cenci and Lundblad, 2006; Ulusoy et al., 2010). However, dissociating changes induced by each compartment independently is complicated by the fact that following destruction of the presynaptic DA neurons, plastic changes of the postsynaptic neurons occur simultaneously (Nadjar et al., 2009; Ulusoy et al., 2010).

4. Positron emission tomography

PET is a nuclear imaging technique which allows *in vivo* estimations of important physiological parameters, such as, glucose metabolism and neuroreceptor binding (Table 1.). In PET, radioisotopes bound to specific tracers are administered to an individual *via* an intravenous (IV) injection. After administration, the radiotracer will decay by positron emission, whereby a positron will be emitted (a particle with the opposite electrical charge but same mass as an electron) and then collide and annihilate with an electron, producing a pair of photons. These photons are subsequently detected by the scintillator in the scanner. These measurements allow the final outcome of estimation of the distribution of the radiotracer over time in the brain. The development of various radiotracers for PET has allowed the *in vivo* assessment of various physiological processes in PD which can be applied for the investigation of pathophysiologic mechanisms underlying both motor and non-motor symptomatology. For example, 18-FDG PET has been implemented to assess glucose brain metabolism in PD patients with dementia (Peppard et al., 1992; Goto et al., 1993) and ^{11}C -PK11195 for microglial activation estimation for monitoring disease progression (Ouchi et al., 2005; Teune et al., 2010).

PET has high sensitivity and specificity for detecting striatal DA deficiency, the core pathological feature of PD, and as such provides an excellent tool for gaining greater understanding of the underlying pathological mechanisms leading to the development of LID in PD. The function of the presynaptic DA system in LID pathogenesis has utilised the tracers; ^{11}C -methylphenidate (MP) which targets the DA transporter (DAT) (Sossi et al., 2007; Troiano et al., 2009), ^{11}C -dihydrotetrabenazine (DHTBZ) which targets the vesicular

monoamine transporter 2 (VMAT2) (Troiano et al., 2009) and Fluorine-18-6-fluoro-L-DOPA (18F-dopa) targeting aminoacid decarboxylase (AADC) PET (de la Feunte-Fernandez et al., 2000). The postsynaptic DA system has been assessed using ¹¹C-raclopride (RAC) targeting D2/D3 receptors (Kishore et al., 1997; Tortonsen et al., 1997; de la Fuente-Fernandez et al., 2001; Pavese et al., 2006; Turjanski et al., 2007) and ¹¹C-SCH23390 which targets D1 receptors (Kishore et al., 1997; Turjanski et al., 2007). Due to emerging evidence that non-DA neurotransmitter systems may play a role in the pathogenesis of dyskinesia tracers such as ¹¹C-diprenorphine (Piccini et al., 1997) and ¹⁸F-L829165 (Whone et al., 2002) have permitted *in vivo* investigation of the neuropeptides, μ , κ , δ opioid sites and NK1 receptors respectively. The adenosinergic system has been investigated with ¹¹C-SCH442416 as a measure of A_{2A} receptors (Ramlackhansingh et al., 2010), the serotonergic system using ¹¹C-DASB as a measure of 5-HT_{1A} binding (Politis et al., 2010b) and the glutamatergic system with ¹¹C-CNS5161 as a marker of activated N-methyl-D-aspartate receptor (NMDA) receptor channels (Ahmed et al., 2010). Knowledge regarding the underlying mechanisms of LID in PD has been greatly advanced by the use of PET imaging tools.

PET tracer	Target	Assessment	Reference
¹¹ C-methylphenidate (MP)	DAT	Presynaptic DA system	Sossi et al., (2007); Troiano et al., (2009)
¹¹ C-dihydrotetrabenazine (DHTBZ)	VMAT2	Presynaptic DA system	Troiano et al., (2009)
Fluorine-18-6-fluoro-L-DOPA (¹⁸ F-dopa)	AADC	Monaminergic systems: -Presynaptic DA system - Noradrenergic system - Serotonergic system	de la Feunte-Fernandez et al., (2000)
¹¹ C-raclopride (RAC)	D2/D3 receptors	Postsynaptic DA system	Turjanski et al., (2007); Kishore et al., (1997); Tortonsen et al., (1997); de la Fuente-Fernandez et al., (2001); Pavese et al., (2006)
¹¹ C-SCH23390	D1 receptors	Postsynaptic DA system	Turjanski et al., (2007); Kishore et al., (1997)
¹¹ C-DASB	5-HT _{1A} receptors	Serotonergic system	Politis et al., (2010a)
¹¹ C-diprenorphine	μ , κ , δ , opioid sites	Opioid system	Piccini et al., (1997)
¹¹ C-SCH442416	Adenosine A _{2A} receptors	Adenosinergic system	Ramlackhansingh et al., (2010)
¹⁸ F-L829165	NK1 receptors	Substance P	Whone et al., (2002)
¹¹ C-CNS 5161	NMDA receptors	Glutamatergic system	Ahmed et al., (2010)

Table 1. PET tracers used to image dyskinesias in PD

5. PET imaging and LID

5.1 Dopaminergic system

The role of DA denervation in the pathogenesis of PD has resulted in the DA neurotransmitter system to have received the most attention in PET studies to date. As both pre- and postsynaptic DA mechanisms are thought to be involved in dyskinesia

pathogenesis and pathophysiology, the opportunity to choose specific tracers targeting each system independently with PET is an important asset of the technique. A study utilising ^{18}F -dopa PET, a measure of the presynaptic DA system by targeting L-aromatic-amino-acid-decarboxylase (AADC) has reported a 28% decrease in presynaptic terminal function in the putamen in PD subjects who had a fluctuating motor response to L-DOPA ('wearing-off' effect) compared to patients who had a stable response to L-DOPA (de la Fuente-Fernandez et al., 2000). The results of this study suggest two things, i) the observed differences between the groups provides support for the 'storage hypothesis'. This hypothesis states that loss of DA terminals, i.e. unable to store and subsequently release DA for use, in the nigrostriatal pathway is responsible for the motor complications observed in PD patients ii) The reported results may reflect an altered 'buffering' capacity of the DA terminals in response to differences in the degree of nigrostriatal damage between groups. However, one limitation of the study relates to the considerable overlap between the two groups studied. This may be indicative of other factors playing a role, such as, postsynaptic mechanisms and increased turnover of DA in the synapse. Another study of presynaptic mechanisms in relation to LID which utilized ^{11}C -methylphenidate (DA transporter [DAT] marker) demonstrated that higher DAT levels were directly related to lower DA turnover and lower changes in the synaptic DA concentration (Sossi et al., 2007). DAT is crucially involved in maintaining consistent levels of DA in the synapse and terminals. Therefore, a decrease in DAT may lead to an increase in DA turnover and higher oscillations in synaptic DA concentration, thus potentially predisposing a PD patient to the occurrence of LID as the disease progresses. A more recent study assessing PD patients with motor fluctuations (27/36 patients presenting LID) using ^{11}C -methylphenidate (MP) and DHTBZ PET in combination, demonstrated that putaminal MP/DTBZ was decreased in the motor fluctuating group compared to PD patients with a stable response to L-DOPA (Troiano et al., 2009). These findings add further support for presynaptic alterations playing a role in the appearance of LID due to continued DAT downregulation leading to increased levels of extracellular DA.

In order to assess the postsynaptic DA mechanisms ^{11}C -SCH23390 and RAC have been used in combination to investigate the availability of the D1 receptor and D2 receptor subtypes respectively, in two groups of PD patients, one with LID and without LID (Kishore et al., 1997; Turjanski et al., 1997). Findings from these studies suggest that postsynaptic DA D1 and D2 mechanisms are possibly not involved in the pathophysiology of LID in PD. The results demonstrate that the mean D1 receptor availability is within normal range in the caudate nucleus and putamen and mean D2 receptor availability in the putamen during the baseline condition in both groups of PD patients. However, mean D2 receptor availability is reduced in both groups in the caudate nucleus by around 15% in each. It may be that the reductions observed in the caudate are a result of disease progression and not due to the development of LID.

However, utilisation of RAC PET in conjunction with L-DOPA challenge can be used in order to assess *in vivo* increases in synaptic DA by measuring decreases of D2 receptor availability (Tedroff et al., 1996; Endres et al., 1997; de la Fuente-Fernandez et al., 2001, 2004). One of the early RAC PET studies revealed a decrease of RAC binding in the putamen by 23% following a single dose of L-DOPA administered IV compared to 10%

decrease in PD patients with a stable response to L-DOPA (Tortenson et al., 1997), which is suggestive of exogenous L-DOPA provoking greater DA release in the putamen of dyskinetic patients than stable responders. Moreover, Unified Parkinson's Disease Rating Scale (UPDRS) scores in the 'off' medication state were inversely correlated with the reduction of putaminal RAC binding. From these data, it appears that as the disease progresses (as evidenced by the decline in motor function measured by the UPDRS), the regulation of DA release following exogenous administration of L-DOPA is impaired. The cause for this is suggested as the impaired regulation of DA back into the synapse after L-DOPA administration is due to the remaining terminals increased DA synthesis and as such, DAT is unable to compensate by reuptaking the excess DA. Another RAC PET study reported that synaptic levels of DA in PD patients with motor fluctuations were three times higher than in those with a stable response to L-DOPA one hour following administration of an L-DOPA challenge (de la Fuente-Fernandez et al., 2001). This result may explain the rapid response to the medication in the motor fluctuating group. Furthermore, stable responders maintained increased DA levels for four hours after L-DOPA administration compared to patients with motor fluctuations, whose synaptic DA levels dropped to baseline ('off') state. More recently, another RAC PET study reported a positive correlation between the presence of LID with increased levels of DA in the synapse (Pavese et al., 2006). More specifically, dyskinetics cases showed significantly decreased levels of putaminal RAC binding reflecting greater levels of synaptic DA, following L-DOPA administration compared to non-dyskinetics. Moreover, the authors correlated L-DOPA induced increases in synaptic DA with corresponding motor scores. It was found that rigidity and bradykinesia but not tremor correlated with DA release in the putamen.

5.2 Opioid system

Opioid neuropeptides are abundant in the basal ganglia as well as the thalamus and association cortex (Haber et al., 1985). Opioid involvement in the pathophysiology of PD has been previously hypothesised from post-mortem studies, however many of these studies are inconsistent with inconclusive and conflicting findings (Rinne et al., 1983; Delay-Goyet et al., 1987; Fernandez et al., 1994). Enkephalin and dynorphin are transmitted by the functionally distinct γ -aminobutyric acid (GABA)ergic pathway transmits these neuropeptides to the globus pallidus (both external [GPe] and internal [GPi]) and have been suggested to play a neuromodulatory role in the control of movements (Austin and Kalavis, 1990). It has been suggested that LID may result due to a reduction in the inhibitory output from the thalamus to the GPi (Crossman, 1990). 6-OHDA-lesioned rats have demonstrated an increase of enkephalin in the GPe and striatum following L-DOPA administration (Engberg et al., 1991; Taylor et al., 1992) and MPTP-treated primates have demonstrated high levels of enkephalin gene expression in the putamen of primates exhibiting LID (Jolkkonen et al., 1995). Altered opioid transmission in the development of LID has been investigated using ^{11}C -Diprenorphine PET (Piccini et al., 1997). This study demonstrated that dyskinetic PD patients had reduced binding in both striatal (caudate nucleus and putamen) and extra-striatal (thalamus and anterior cingulate) regions compared to PD patients who had a stable response to L-DOPA and no LID. Little is known regarding impact of a dysfunctional opioid system on LID development, however, these results are suggestive that an involvement is

possible, considering it is established that the opioid system is involved in the pathophysiology of PD.

5.3 NK1 receptors

¹⁸F-L829165 is a selective marker of Neurokinin-1 (NK1) receptor availability. NK1 receptors belong to the family of neuropeptides called Tachykinins and can be found in both the central and peripheral nervous system. A more recent, although, preliminary study has been reported a reduction in thalamic NK1 availability in dyskinetic PD patients while remaining within the normal range in PD with a stable response to L-DOPA (Whone et al., 2002). Overall, these *in vivo* findings are suggestive that the presence of elevated levels of endogenous neuropeptides in the basal ganglia of dyskinetic PD patients may be, in part, responsible for the development of LID.

5.4 Adenosinergic system

There is neurochemical evidence that A_{2A} receptors functionally appose the action of D2 receptors on GABAergic striatopallidal neurons (Ferre and Fuxe, 1992; Ferre et al., 1993; Fuxe et al., 1993) raising the possibility that A_{2A} antagonists may be able to contribute to the anti-parkinsonian therapeutic benefit observed in DA replacement therapy. Indeed, animal studies have shown that lesioning one side of the DA nigrostriatal pathway by 6-OHDA revealed that blockade of A_{2A} receptors markedly increased the number of contralateral rotations induced by a threshold dose of L-DOPA or by stimulation of DA receptor stimulation (Pinna et al., 1996; Pollack and Fink, 1996; Fenu et al., 1997; Le Moine et al., 1997). Thus blockade of A_{2A} receptors and as such potentiating DA transmission may contribute to the restoration of motor impairment observed in animal models of PD.

Early clinical data suggests that A_{2A} agonists do not suppress LID in PD patients once LID is established (Hauser et al., 2003), however, preclinical data suggests that a possible role of A_{2A} blockade in the reduction of initial LID emergence when combined with L-DOPA (Pinna et al., 2001). However, the potential therapeutic benefit of A_{2A} agonists are yet to be fully delineated as conflicting evidence has been reported (Lundblad et al., 2003).

To date only one preliminary imaging study has been undertaken to assess the potential role of A_{2A} receptors in LID pathogenesis. The recent study utilised ¹¹C-SCH442416 PET as a marker of A_{2A} receptor function in six PD patients with LID, six PD patients without LID and three healthy controls (Ramackhansingh et al., 2010). Both PD groups withdrew from medication prior to the scan. Spectral analysis was used to calculate regional volumes of A_{2A} receptor binding distribution in the striatum and thalamus. Results showed a significant increase of striatal A_{2A} binding in the PD patients with LID compared to the PD group without LID and healthy controls which demonstrated a similar degree of striatal A_{2A} binding. Thalamic A_{2A} binding was similar across all three groups. The authors concluded that their results provide a rationale for the use of A_{2A} receptor agonists in the clinical management of LID.

5.5 Glutamatergic system

Glutamate is an excitatory neurotransmitter in the basal ganglia which acts through ionotropic, amino acid derivative, N-Methyl-D-aspartate (NMDA) and the non-NMDA transmembrane receptors for glutamate, -amino-3-hydroxy-5-methyl-4-isoxazolepropionic

acid (AMPA) and kainite and G-protein coupled metabotropic receptor subtypes. Within the striatum, NMDA receptors mostly contain the subtypes, NR1, NR2A and NR2B subtypes (Küppenbender et al., 2000). Animal models of PD, including the 6-OHDA-lesioned rat model and MPTP-treated primates, have demonstrated an increase of glutamate neurotransmission in association with hyperphosphorylation of these receptor subtypes and the development and maintenance of LID.

To date, only one study has attempted to investigate abnormal glutamate function *in vivo* in PD patients in relation to LID (Ahmed et al., 2010). ^{11}C -CNS 5161 PET binds to the MK801 site in the activated voltage-gated ion channels with high affinity (Biegon et al., 2007), and as such, striatal and cortical NMDA glutamate ion channel activity can be assessed in relation to LID. A recent study of 18 PD patients divided into those with LID and those with a stable response to L-DOPA underwent two ^{11}C -CNS 5161 PET scans, one while 'ON' following administration of L-DOPA and another while functionally 'OFF' any DA medication. Results showed reduced binding in the caudate, putamen and motor cortex of the stable responders following administration of L-DOPA. This is in contrast to the LID PD group suggesting that there is a relatively enhanced glutamate receptor activity in the motor areas of this group. The authors suggest that their results justify a rationalization of glutamate antagonist use in the attempt to improve LID in PD patients. However, the authors accept the study is limited by the fact that ^{11}C -CNS 5161 is a selective agonist for NMDA receptors therefore does not provide any information regarding other glutamate receptor subtypes. Although they do suggest that it is likely that other receptor subtypes also become sensitive to L-DOPA.

5.6 Serotonergic system

L-DOPA acts in the early stages of the disease by being taken up into the spared DA terminals, whereby it is converted to DA, stored in synaptic vesicles and then released in an activity-dependent manner. As the disease progresses, there are less DA terminals available for this conversion and as such, it has been suggested that other cell types may become involved in the decarboxylation of L-DOPA in the advanced disease. Serotonergic neurons express AADC and vesicular monoamine transporter 2 (VMAT-2), which are involved in the conversion of L-DOPA and which is involved in the storage of DA respectively (Arai et al., 1994, 1995, 1996). Moreover, serotonin neurons in the dorsal and median raphe nuclei innervate the striatum (Lavoie and Parent, 1990; Nicholson et al., 2002). The presence of AADC and VMAT-2 in serotonin neurons provides the possible opportunity for L-DOPA derived DA to be formed, stored and released, thus acting as a 'false neurotransmitter' in serotonergic terminals. However, serotonergic neurons are unable to handle DA release in a regulated manner. Autoreceptor-mediated feedback control and reuptake *via* DAT maintain extracellular DA levels within a narrow physiological range in the DA synapses. The process of DA reuptake allows effective elimination of excess DA from the synaptic cleft, with the D2 autoreceptor maintaining the release from DA terminals in response to changes in the extracellular DA levels (Venton et al., 2003; Cragg et al., 2004) within the desired range. As serotonin neurons do not possess this autoregulatory mechanism, any DA released from serotonergic terminals is likely to generate excessive swings in extracellular levels of DA in response to L-DOPA administration (Carta et al., 2007). To date, the possible role of serotonin in LID has been studied primarily in animal models of PD (Ng et al., 1970, 1971;

Hollister et al., 1979; Lavoie and Parent, 1990; ; Arai et al., 1994, 1995, 1996; Tanaka et al., 1990; Brotchie et al., 2000; Lugnier et al., 2000; Obeso et al., 2000; Nicholson et al., 2002; Maeda et al., 2005; Carta et al., 2007) with only one *in vivo* preliminary results being reported thus far (Politis et al., 2010b).

Animal studies utilising 6-OHDA-lesioned rat (Carta et al., 2007; Munoz et al., 2009) and MPTP-treated primates (Munoz et al., 2008) has reported an almost-complete abolition of the dyskinetic movements induced by chronic L-DOPA treatment when DA release is blocked from the serotonin neurons using 5-HT_{1A} and 5-HT_{1B} autoreceptor agonists without compromising the therapeutic benefit of L-DOPA on motor symptoms. Furthermore, the authors demonstrated that the combination of 5-HT_{1A} and 5-HT_{1B} agonists prevented the development of LID in MPTP-treated primates (Munoz et al., 2008). Therefore, the authors suggest that combining 5-HT_{1A} and 5-HT_{1B} agonists may be a favourable treatment strategy for PD patients.

Clinical trials have been undertaken testing the 5-HT_{1A} agonist, Sarizotan in more than 1000 PD patients (PADDY-1 and PADDY-2). Unfortunately these trials were unable to meet their primary endpoint which may have been a result of the low dose (1mg) administered in the phase III study compared to the dose (2 – 5mg) administered and proven effective in the phase II study (Bara-Jimenez et al., 2005).

Overall, it appears that there may be a competition for storage at the serotonergic synapse, between L-DOPA derived DA and serotonin. It is suggested that this competition may lead to a depletion in serotonin content thus an over-activation of serotonin terminals which are attempting to compensate for the reduced binding to the presynaptic serotonin autoreceptors. Subsequently there is an excessive release of DA from these neurons, triggering the LID.

To date only preliminary data has been reported relating the serotonergic system to the pathophysiology of LID in PD patients with PET (Politis et al., 2010b). The authors conducted a RAC PET study and medication challenges with supratherapeutic doses of L-DOPA and Buspirone (5-HT_{1A} agonist) in 16 PD patients with LID and 12 PD patients with a stable response to L-DOPA therapy. The authors aimed to investigate the possibility that relatively preserved striatal 5-HT terminals may cause or aggravate LID by mishandling exogenous L-DOPA and releasing DA as a false neurotransmitter.

Dyskinetic patients demonstrated an 18% decrease in putaminal RAC binding compared to an 8% reduction in the stable PD responder group. This result reflects an increase of DA synaptic turnover in the dyskinetic group as also shown in previous studies (de la Fuente-Fernandez et al., 2001; Pavese et al., 2006). However, administration of 5-HT_{1A} agonist, buspirone preceding the administration of L-DOPA in the dyskinetic PD group revealed a normalization of putaminal synaptic DA at comparable levels to those of the stable PD responders as this was judged by the 12% decrease of their putaminal RAC binding. The authors also demonstrated that clinically, the administration of L-DOPA and Buspirone in combination significantly attenuated LID. Therefore, the authors suggest that the use of 5-HT agonists, which dampen the transmitter release from 5-HT neurons, alleviating excessive synaptic DA levels and thus attenuating LID, is justified.

6. Dyskinesias following neural transplantation

The progressive decline of the clinical course of PD and the resulting motor complications of LID has resulted in more sophisticated therapeutic approaches in tackling PD symptomatology and medication side-effects. One such approach has been

implemented in the way of DA-rich fetal ventral mesencephalic (VM) tissue transplantation in the striatum of PD patients. The rationale for such a procedure is based on the hypothesis that PD is the result of DA denervation in the nigrostriatal pathway and striatum and that transplanation of DA neurons could restore DA levels and reverse motor disability. Clinical trials on VM transplantation have been undertaken in the past two decades. Unfortunately results regarding motor symptom relief have been inconsistent with many patients developing motor complications termed GIDs, whereby these patients appear to develop these involuntary movements whilst 'OFF' their DA medication. It is not currently understood if GIDs share the same pathophysiology and pathogenesis as LID induced by L-DOPA therapy. It has been suggested that GIDs develop as a result of graft fiber outgrowth causing an increase in DA release (Freed et al., 2001) or due to an underadequate degree of DA release as DA reinnervation has failed (Ma et al., 2002).

Animal studies may have provided an insight in to the pathogenesis of GIDs in PD patients following VM tissue transplantaion. DA rich grafts have been shown to improve LID in animals (Lee et al., 2000). However, transplantation of fetal serotonergic neurons into the striatum of 6-OHDA-lesioned rats has been shown to exacerbate LID by up to 70% compared to pre-transplantation scores (Carlsson et al., 2007, 2009). Considering the evidence that other cells may be involved in the conversion, storage and release of DA, it is possible that this effect occurs as a consequence of abnormal handling of DA. Recent work has shown that serotonin neurons are involved in the development of GIDs despite the successful recovery of motor function. Utilising ^{11}C -DASB PET, a selective marker for serotonin transporter (SERT) binding, in two patients who developed GID following neural transplantation, it has been demonstrated that PD patients developing GIDs following VM tissue transplantation, exhibited excessive serotonergic innervation in the grafted striatum (Politis et al., 2010c). Furthermore, following the administration of the 5-HT_{1A} buspirone, the GIDs were markedly reduced indicating that the motor complication arose from serotonergic hyperinnervation. It is not known, however, if the mechanisms underlying GID are the same for LID, but nonetheless, this study provides the first *in vivo* evidence for the serotonergic hypothesis in the development of motor complications in PD.

7. Conclusion

Risk factors of LID development appear to be relatively established including degree of DA denervation, L-DOPA dose and duration of L-DOPA therapy. The advent of PET imaging has enabled much progress in understanding the mechanisms underlying LID. LID likely results from a combination of factors including, alteration of various neurotransmitter systems, abnormal synaptic plasticity and an altered firing pattern within the basal ganglia. LID is a troublesome side effect of DA therapy and currently there is no treatment. As such, it results in decreased quality of life for PD patients and in increased health care costs. Although the DA system appears to be primarily implicated in the PD pathological process, results from animal and *in vivo* studies provide evidence that non-DA neurotransmitter systems may have a role in the pathogenesis of LID. Manipulation of these systems may offer an alternative therapeutic approach in abating LID and preventing their initial

development. Furthermore, as more sophisticated therapeutic approaches for alleviating the symptoms of PD are considered, it is imperative that these potential motor complications are fully understood in order to avoid their development. The use of PET imaging, although expensive and not widely available, provides an excellent tool for predictive validity of *in vivo* patient studies which will ultimately minimise the risk of failure in future clinical and cell therapy trials.

8. References

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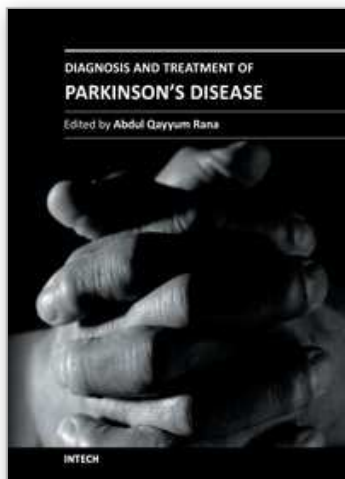
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Diagnosis and Treatment of Parkinson's Disease

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Parkinson's disease is diagnosed by history and physical examination and there are no laboratory investigations available to aid the diagnosis of Parkinson's disease. Confirmation of diagnosis of Parkinson's disease thus remains a difficulty. This book brings forth an update of most recent developments made in terms of biomarkers and various imaging techniques with potential use for diagnosing Parkinson's disease. A detailed discussion about the differential diagnosis of Parkinson's disease also follows as Parkinson's disease may be difficult to differentiate from other mimicking conditions at times. As Parkinson's disease affects many systems of human body, a multimodality treatment of this condition is necessary to improve the quality of life of patients. This book provides detailed information on the currently available variety of treatments for Parkinson's disease including pharmacotherapy, physical therapy and surgical treatments of Parkinson's disease. Postoperative care of patients of Parkinson's disease has also been discussed in an organized manner in this text. Clinicians dealing with day to day problems caused by Parkinson's disease as well as other healthcare workers can use beneficial treatment outlines provided in this book.

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