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From the cell to the clinic: A comparative review of the partial D_2/D_3 receptor agonist and α_2-adrenoceptor antagonist, piribedil, in the treatment of Parkinson's disease

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ABSTRACT

Though L-3,4-dihydroxyphenylalanine (L-DOPA) is universally employed for alleviation of motor dysfunction in Parkinson's disease (PD), it is poorly-effective against co-morbid symptoms like cognitive impairment and depression. Further, it elicits dyskinesia, its pharmacokinetics are highly variable, and efficacy wanes upon long-term administration. Accordingly, "dopaminergic agonists" are increasingly employed both as adjuncts to L-DOPA and as monotherapy. While all recognize dopamine D_2 receptors, they display contrasting patterns of interaction with other classes of monoaminergic receptor. For example, pramipexole and ropinirole are high efficacy agonists at D_2 and D_3 receptors, while pergolide recognizes D_1, D_2 and D_3 receptors and a broad suite of serotonergic receptors. Interestingly, several antiparkinson drugs display *modest* efficacy at D_2 receptors. Of these, piribedil displays the unique cellular signature of: 1), signal-specific *partial* agonist actions at dopamine D_2 *and* D_3 receptors; 2), *antagonist* properties at α_2-adrenoceptors and 3), *minimal* interaction with serotonergic receptors. Dopamine-deprived striatal D_2 receptors are super-sensitive in PD, so partial agonism is sufficient for relief of motor dysfunction while limiting undesirable effects due to "over-dosage" of "normosensitive" D_2 receptors elsewhere. Further, α_2-adrenoceptor antagonism reinforces adrenergic, dopaminergic and cholinergic transmission to favourably influence motor function, cognition, mood and the integrity of dopaminergic neurones. In reviewing the above issues, the present paper focuses on the distinctive cellular, preclinical and therapeutic profile of piribedil, comparisons to pramipexole, ropinirole and pergolide, and the core triad of symptoms that characterises PD-motor dysfunction, depressed mood and cognitive impairment. The article concludes by highlighting perspectives for clarifying the mechanisms of action of piribedil and other antiparkinson agents, and for optimizing their clinical exploitation.

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Abbreviations: ACh, acetylcholine; Akt, atypical kinase; AR, adrenoceptor; BDNF, brain derived neurotrophic factor; COMT, catechol-Ortho-methyltransferase; DA, dopamine; ERK, extracellular regulated kinase; FCX, frontal cortex; fMRI, functional magnetic resonance imaging; GABA, γ-aminobutyric acid; GIRK, G-protein coupled inwardly rectifying potassium channel; GPCR, G-protein coupled receptor; GPE/I, globus pallidus externa/interna; GRK, G-protein receptor kinase; GSK-3β, glycogen synthase kinase-3β; LC, locus coeruleus; L-DOPA, L-3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydroxypyridine; NA, noradrenaline; NBM, Nucleus basalis of Meynert; PD, Parkinson's disease; SNPC/R, substantia nigra pars compacta/reticulata; STN, subthalamic nucleus; [^{35}S]GTPγS, [^{35}S]guanosine triphosphateγS; UPDRS, Unified Parkinson's Disease Rating Scale; WCST, Wisconsin Card Sorting Test.

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1. Introduction: major features of Parkinson's disease and its treatment

1.1. Principal characteristics of Parkinson's disease

1.1.1. A complex aetiology: environmental and genetic risk factors

Parkinson's disease (PD) is a progressive and severe neurodegenerative disorder epitomised by a massive loss of dopaminergic neurones from the substantia nigra, pars compacta (SNPC) (Hornykiewicz and Kish, 1986; Agid et al., 1989; Stoessl, 2007; Olanow et al., 2009b; Hawkes et al., 2010). Other dopaminergic pathways are also impacted, together with ascending adrenergic and serotonergic networks, frontocortical cholinergic projections, and a diversity of neuronal circuits located not only in the brain (from the cortex to the medulla), but even in the spinal cord and sympathetic nervous system (Sian et al., 1999; Braak et al., 2003; Au et al., 2006; Brooks and Piccini, 2006; Francis and Perry, 2007; Rommelfanger and Weinshenker, 2007; Rommelfanger et al., 2007; Sulzer, 2007; Smith and Villalba, 2008; Djaldetti et al., 2009; Ferrer, 2009). These pathological events are triggered by a poorly understood cluster of environmental risks (such as pesticides, neurotoxins, high fat diet, cerebral trauma and viral infection) superimposed upon a complex background of genetic vulnerability. Interestingly, amongst genes incriminated as risk factors and/or associated with cases of inherited, "familial" PD, several interact and are related to mitochondrial function/oxidative stress and/or ubiquitination/proteosome function: notably SNCA (α-synuclein) and—more commonly—leucine-rich repeat kinase 2 ("LRRK2"), which are autosomal-dominant, and "PINKI" and "PARK2" (parkin) which are autosomal-recessive (De Lau and Breteler, 2006; Greggio and Singleton, 2007; Sulzer, 2007; Biskup et al., 2008; Hardy et al., 2009; Lesage and Brice, 2009; Satake et al., 2009).

1.1.2. Motor dysfunction, depressed mood and cognitive impairment

PD is characterised by a profound disruption of motor function, including the cardinal symptoms of bradykinesia, tremor, rigidity, perturbed gait and postural instability (Agid et al., 1989; Jankovic, 2008; Hawkes et al., 2010; Truong and Wolters, 2009). In addition, Parkinsonian patients can manifest a remarkably broad suite of other symptoms including: anxiety and apathy (Section 9.2); sexual dysfunction; sleep disorders, other nocturnal disturbances and excessive daytime sleepiness; psychosis and compulsive behaviors; dysarthria; hyp/anosmia; pain, autonomic dysfunction, genitourinary complaints and osteoporosis (Garcia-Borreguero et al., 2003; Grandas and Iranzo, 2004; Aarsland et al., 2007; Djaldetti and Malamed, 2007; Mehta et al., 2008; Invernizzi et al., 2009; Kirsch-Darrow et al., 2009; Matinolli et al., 2009; Verbaan et al., 2009; Sakakibara et al., 2010).

Co-morbid depression, which not infrequently precedes motor disability and has a prevalence rate of some 30–50% (Leentjens et al., 2003; Ravina et al., 2007; Truong and Wolters, 2009), can severely disrupt social and professional activities (Rojo et al., 2003; Rahman et al., 2008; Reijnders et al., 2008). Depressed affect at least partially reflects a distinctive pattern of pathological events directly impacting mood, and involving a perturbation not only of dopaminergic transmission but also of serotonergic, adrenergic and other neurotransmitter networks (Jellinger, 1999; Braak et al., 2003; McDonald et al., 2003; Brooks and Piccini, 2006; Rommelfanger et al., 2007; Rommelfanger and Weinshenker, 2007; Lemke, 2008; Rowe et al., 2008; Taylor et al., 2009). The depressive symptoms of PD are *not*, then, just an epiphenomenon of chronic motor dysfunction, though they are especially pronounced during akinetic ("off") episodes and in patients with advanced PD (Leentjens et al., 2003; Miyasaki et al., 2006; Reijnders et al., 2008).

Depressed mood negatively impacts mnemonic function (Weintraub et al., 2006; Kummer et al., 2009b) and, like depression, cognitive deficits in PD are: 1), very common and 2), reflect pathological events *differing* from those disrupting motor function. Cognitive impairment often anticipates motor dysfunction and becomes progressively more pronounced—not infrequently commencing with "mild cognitive impairment" to culminate in dementia (Dubois and Pillon, 1997; Janvin et al., 2006; Miyasaki et al., 2006; Emre et al., 2007; Merims and Freedman, 2008; Rowe et al., 2008; Bosboom et al., 2009; Truong and Wolters, 2009). Cognitive dysfunction is wide-ranging and heterogeneous, including deficits in procedural learning and interrelated impairments in speed of processing and reaction time (Gauntlett-Gilbert and Brown 1998; Sawamoto et al., 2007; Machado et al., 2009), as well as poor visuospatial and verbal memory (Henry and Crawford, 2004; Lewis et al., 2005; Vale, 2008; Jokinen et al., 2009; Williams-Gray et al., 2009). Moreover, in line with the functional disruption of frontocorticostriatal (and, in advanced PD, parietotemporal) circuits (Borod et al., 2003; Owen, 2004; Zgaljardic et al., 2006; Monchi et al., 2007), attention, working memory and executive function (planning, concept formation and cognitive flexibility) are compromised (Lewis et al., 2005; Chudasama and Robbins, 2006; Moustafa et al., 2008; Vale, 2008; Farid et al., 2009; Price and Shin, 2009; Williams-Gray et al., 2009), as well as social cognition and "theory of mind" (Saltzman et al., 2000; Péron et al., 2009).

Thus, the motor dysfunction of PD is generally accompanied by depressed affect and cognitive impairment, comprising the triad of deficits that most profoundly interfere with patient quality of life (Gallagher and Schrag, 2008; Merims and Freedman, 2008; Rahman et al., 2008; Reijnders et al., 2008; Vale, 2008).

1.2. Current therapy of Parkinson's disease: L-DOPA and dopaminergic agonists

For many years, the DA precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), has been employed as standard treatment for PD, and it is highly effective in the restitution of most components of motor performance (Rascol et al., 2003; Olanow et al., 2004, 2009b; Horstink et al., 2006; Schapira et al., 2006; Riederer et al., 2007; Jenner, 2008b; Simuni et al., 2009a,b). L-DOPA does not, however, greatly alleviate tremor, it is poorly active against postural instability and freezing of gait, and co-morbid symptoms like depression, cognitive impairment, perturbed sleep and sensory dysfunction are little improved (Sethi, 2008; Olanow et al., 2009b) (Sections 9.1 and 9.2). Further, the pharmacokinetics of L-DOPA are highly variable and it elicits marked dyskinesias. Finally, after a "honeymoon" period of 5 years or so, efficacy begins to wane and abrupt transitions between phases of effective control ("ON") and lack of efficacy ("OFF") become seriously disruptive to patients (Olanow et al., 2004, 2009b; Horstink et al., 2006; Nyholm, 2006; Schapira et al., 2006; Riederer et al., 2007).

The above observations underline the importance of directly-acting dopaminergic agonists like pramipexole, ropinirole and pergolide in the management of (early) PD. Upon co-administration with L-DOPA, they have been consistently shown to reduce the risk of dyskinesia while respecting therapeutic efficacy (Clarke and Guttman, 2002; Foley et al., 2004; Goetz et al., 2005; Gallagher and Schrag, 2008; Baker et al., 2009; Olanow et al., 2009b; Simuni et al., 2009a,b). Moreover, though it is questionable whether dopaminergic agonists are as efficacious as L-DOPA when employed as monotherapy, their long-term efficacy in the control of motor symptoms is well-established. Accordingly, in particular in young patients, most neurologists favour the use of an agonist when initiating therapy of newly-diagnosed PD: this allows the introduction of L-DOPA to be