Pharmacology & Therapeutics 245 (2023) 108392

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

The complex molecular pharmacology of the dopamine D_2 receptor: Implications for pramipexole, ropinirole, and rotigotine

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ARTICLE INFO

Available online 21 March 2023

Associate editor: S.J. Enna

Keywords:
Dopamine
Pramipexole
Ropinirole
Rotigotine
Agonists
D_2 receptor

ABSTRACT

With L-DOPA, dopamine agonists such as pramipexole, ropinirole and rotigotine constitute key therapeutic options for the management of motor symptoms of Parkinson's disease. These compounds exert their beneficial effect on motor behaviours by activating dopamine D_2-class receptors and thereby compensating for the declining dopaminergic transmission in the dorsal striatum. Despite a strong similarity in their mechanism of action, these three dopamine agonists present distinct clinical profiles, putatively underpinned by differences in their pharmacological properties. In this context, this review aims at contributing to close the gap between clinical observations and data from molecular neuropharmacology by exploring the properties of pramipexole, ropinirole and rotigotine from both the clinical and molecular perspectives. Indeed, this review first summarizes and compares the clinical features of these three dopamine agonists, and then explores their binding profiles at the different dopamine receptor subtypes. Moreover, the signalling profiles of pramipexole, ropinirole and rotigotine at the D_2 receptor are recapitulated, with a focus on biased signalling and the potential therapeutic implications. Overall, this review aims at providing a unifying framework of interpretation for both clinicians and fundamental pharmacologists interested in a deep understanding of the pharmacological properties of pramipexole, ropinirole and rotigotine.

Contents

Abbreviations: 6-OHDA, 6-hydroxydopamine; AADC, amino-acid decarboxylase; BDNF, brain-derived neurotrophic factor; BRET, bioluminescence resonance energy transfer; CHO, Chinese hamster ovary; COMT, catechol-O-methyl transferase; EDS, excessive daytime sleepiness; GBL, gamma-butyro-lactone; GDNF, glial cell line-derived neurotrophic factor; GIRK, G protein-coupled inwardly-rectifying potassium channels; GRK, GPCR kinase; GSK3β, glycogen synthase kinase 3 beta; HAM-D, Hamilton depression rating scale; HEK, human embryonic kidney; ICDs, impulse control disorders; MAO-B, monoamine oxidase B; MAPK, mitogen-activated protein kinase; MFB, medial forebrain bundle; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSN, medium spiny neurons; PD, Parkinson's disease; PP2A, protein phosphatase 2A; UPDRS, unified PD rating scale.

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https://doi.org/10.1016/j.pharmthera.2023.108392
0163-7258/

1. Introduction

Along with L-DOPA, the pharmacological treatment of Parkinson's disease (PD) patients currently relies on the prescription of dopamine agonists, notably pramipexole, ropinirole, and rotigotine. By activating dopamine receptors and thus compensating for dopamine deficits, these drugs are effective at relieving both motor (bradykinesia, akinesia, resting tremor, muscular rigidity, and postural instability) and non-motor symptoms (depression, dementia and sleep dysfunction), with a globally positive impact on the quality of life of patients (Armstrong & Okun, 2020). While L-DOPA is proven efficient for the treatment of PD at every stage of the disease, and therefore constitutes the mainstay treatment for PD (Gray et al., 2014), the long-term administration of L-DOPA is characterized by the progressive loss of clinical effectiveness and a considerable array of adverse effects, mainly consisting in dyskinesias and motor fluctuations, referred to as "On-Off oscillations". As the loss of dopaminergic neurons progresses, these undesired effects arise from the unfavourable pharmacokinetic profile of L-DOPA, of which half-life is narrowed by its biotransformation by peripheral amino-acid decarboxylase (AADC), monoamine oxidase B (MAO-B), and catechol-O-methyl transferase (COMT) enzymes together with being influenced by food intake. Hence, L-DOPA is systematically administered in combination with a peripheral inhibitor of AADC (either carbidopa or benserazide) to prolong its half-life and decrease side effects caused by its biotransformation into dopamine before accessing the central nervous system. Besides, the occurrence of motor fluctuations and dyskinesias can be reduced by combining L-DOPA with centrally-acting MAO-B inhibitors (selegiline, rasagiline, safinamide), or COMT inhibitors that mostly act peripherally (entacapone and opicapone) (Armstrong & Okun, 2020; Poewe et al., 2017).

However, the opportunity of relieving both motor and non-motor symptoms without the cumbersome implementation of diverse pharmacotherapies in complement to L-DOPA presents remarkable clinical interest. Thus, the discovery of compounds capable of reinforcing dopaminergic activity first reported in the seventies sparked remarkable interest in the neuroscience community. Realizing that the ergot-derived compound bromocriptine -at the time used for the treatment of galactorrhoea, pituitary tumours, and fertility issues- could affect neuronal transmission comparably to dopamine (Corrodi, Fuxe, Hökfelt, Lidbrink, & Ungerstedt, 1973; Hökfelt & Fuxe, 1972) paved the way for the characterization of ergot-derived compounds as putative dopamine agonists. Given that the dopamine depletion hypothesis for the neuropathology of PD was gaining ground in the medical community (Ehringer & Hornykiewicz, 1960), bromocriptine and other ergot derivatives such as piribedil and lisuride (respectively commercialized as vasodilator and antimigraine drugs) were rapidly adopted as antiparkinsonian agents (Calne et al., 1974; Lieberman et al., 1979; Sweet, Wasterlain, & McDowell, 1974). Together with the repurposing of the emetic compound apomorphine, the later development of original compounds derived from the ergot backbone, namely cabergoline and pergolide, contributed to enrich the pharmacotherapeutic arsenal against PD with dopamine-mimicking drugs capable of offering an alternative or a complement to L-DOPA (Horowski, 2007).

The detailed analysis of the pharmacodynamic properties of dopamine agonists evidenced that their clinical efficacy relies on their capacity to bind and activate the dopamine D_1 and D_2 receptors, respectively expressed by striatal medium spiny neurons (MSN) of the direct and indirect pathways of motor control (Gerlach et al., 2003). However, the activity of these compounds at non-dopamine receptors was correlated with the occurrence of adverse effects of adrenergic and serotoninergic nature, reducing patient compliance. Importantly, the $5HT_{2B}$ agonism presented by cabergoline and pergolide was associated with the establishment of potentially lethal fibrotic heart valve reactions, limiting the use of these compounds as anti-PD agents (Antonini & Poewe, 2007; Peralta et al., 2006; van Camp et al., 2004). Nevertheless, accumulating evidence pointed towards selective dopamine agonists as significantly effective therapeutic options, in monotherapy but most frequently in combination with L-DOPA, enabling the stabilization of its dosage and the reduction of On-Off oscillations. Thus, the call for the introduction of a novel generation of dopamine agonists devoid of any significant non-dopaminergic receptor binding, providing a safer alternative to ergot-derived compounds, appeared as a priority in drug development. This medical need was first met in the late '90s with the market approval of pramipexole and ropinirole, and later with rotigotine.

Pramipexole was synthesized during the quest for an antipsychotic compound capable of reducing dopamine synthesis and release by acting at dopamine presynaptic autoreceptors (Mierau & Schingnitz, 1992; Schneider & Mierau, 1987). As both the amino-hydroxytetraline backbone of apomorphine and aminothiazole derivatives appeared as endowed with specific presynaptic dopaminergic activity, Schneider et al synthesized the 2,6-diaminotetrahydro-benzothiazole (Fig. 1 A), intending to fuse both backbones in a compound later known as pramipexole (Schneider & Mierau, 1987). Such compound presented the desired virtues of presynaptic dopamine agonism, notably the reduction of gamma-butyrolactone (GBL)-induced acceleration in dopamine synthesis in rat striatum and the inhibition of alpha-methyltyrosine-induced reduction in dopamine synthesis, and so with a higher potency as compared to apomorphine (Mierau & Schingnitz, 1992; Schneider & Mierau, 1987). Moreover, these effects were assigned to D_2 receptor binding, as the effects were reversed in presence of haloperidol, but not by the specific D_1 receptor antagonist SCH 23390 (Mierau & Schingnitz, 1992). Pramipexole also potently inhibited exploratory locomotor behaviour in mice, while showing postsynaptic agonism only in animal models of dopamine depletion, causing contralateral rotations in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys or in rats undergoing unilateral lesion of the medial forebrain bundle (MFB) (Mierau & Schingnitz, 1992). Further analyses showed that these presynaptic effects mediated by pramipexole are not solely related to its activity at the D_2 receptor, as first hypothesized, but rather to its high affinity binding to the D_3 receptor, largely expressed in presynaptic compartments (Mierau et al., 1995).

Ropinirole (Fig. 1 B), was initially developed for the treatment of hypertension, following the observation that indolone-derived D_2 receptor agonists could relax smooth muscles and induce vasodilatation (Gallagher, Lavanchy, Wilson, Hieble, & DeMarinis, 1985). However, its high affinity and selectivity for D_2 receptor (Ki of 29 nM when measured in human caudate), together with the absence of D_1 receptor binding (commonly associated with the establishment of dyskinesias, offsetting the positive effect on locomotion of D_1 receptor binding) and negligible adrenergic and serotoninergic activities made it a suitable candidate for the treatment of PD (Eden et al., 1991). Indeed, it proved effective at inducing contralateral rotations in mice lesioned with 6-hydroxydopamine (6-OHDA), and reversed MPTP-induced motor deficits in marmosets more efficiently than bromocriptine. At variance with L-DOPA, ropinirole did not cause significant emesis and presented increased long-term efficacy (Eden et al., 1991). Taken together, these preclinical observations paved the way for the clinical evaluation of ropinirole as an antiparkinsonian agent.

At variance with pramipexole and ropinirole, rotigotine (Fig. 1 C) was purposely designed as antiparkinsonian drug, namely through the reverse engineering of the chemical structure of apomorphine. In detail, the isolation of the 2-aminotetraline moiety of apomorphine was associated with the development of a series of compounds characterized by potent dopamine receptor activation. Among these, N-0437, was characterized by the replacement of a phenyl ring for a thiophene group that further enhanced D_2 binding affinity, reaching unprecedented values (Ki of 0.146 nM) on porcine pituitary tissue when competing with tritiated spiperone (Horn et al., 1985). During in vivo tests, N-0437 presented potent dopaminergic activity, both

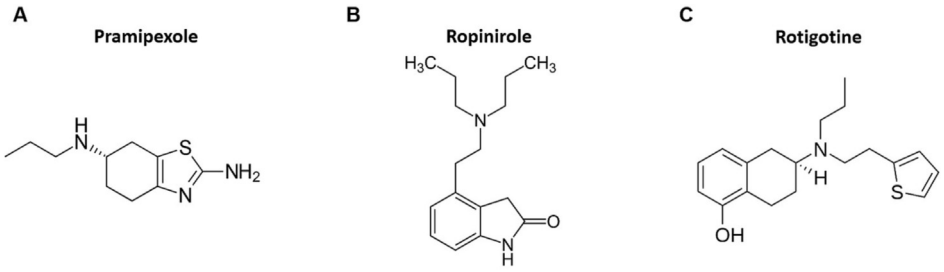

Fig. 1. Chemical structure of the non-ergot dopamine agonists pramipexole (A), ropinirole (B), and rotigotine (C).

presynaptically (assessed by measuring the decrease in the production of the dopamine catabolite homovanillic acid and the reversal of GBL-induced L-DOPA synthesis) and postsynaptically, appraised by the rescue of reserpine-induced hypolocomotion in mice and by the re-establishment of stereotyped behaviour after dopamine depletion caused by methyltyrosine treatment in rats (van der Weide, de Vries, Tepper, & Horn, 1986). Importantly, the (-) enantiomer of N-0437, first referred to as N-0923 and then as rotigotine, presented even more promising anti-PD properties in 6-OHDA lesioned rats, together with countering MPTP-caused hemiparkinsonism in monkeys more potently than bromocriptine (Belluzzi, Domino, May, Bankiewicz, & McAfee, 1994). As such, rotigotine exhibited promising therapeutic features in the context of PD. However, pharmacokinetic studies in rats indicated that rotigotine undergoes extensive first-pass metabolism, making it unsuitable for oral administration (Swart & de Zeeuw, 1993). Nevertheless, the high potency and lipophilic features of rotigotine turned this compound eligible for transdermal administration, enabling stable plasma levels and thereby supporting a persistent dopaminergic stimulation for up to 24 hours (Elshoff, Cawello, Andreas, Mathy, & Braun, 2015; Metman et al., 2001). The clinical use of pramipexole, ropinirole and rotigotine enriched the therapeutic arsenal dedicated to countering PD symptoms with three safe and effective compounds. However, given the wealth of available anti-PD agents and the complexity of this neurological disease, prescribing patients with the most appropriate compound is by no means evident. Moreover, the apparent overlap of pharmacological properties across dopamine agonists may result in information redundancy, with detrimental consequences on the decision-making process in which clinicians are engaged on a daily basis.

In this context, this review aims at reconciling the currently available literature concerning the pharmacodynamic and therapeutical properties of pramipexole, ropinirole and rotigotine. Furthermore, clinical evidence will be discussed in relation to observations derived from molecular pharmacology studies. Hence, by adopting both clinical and biochemical standpoints, we aim at characterizing the multifaceted aspects of non-ergot dopamine agonists, shedding light on the peculiarities that characterize each of these compounds.

2. Clinical features of dopamine agonists

2.1. Treatment of PD motor symptoms

The drug registration of pramipexole, ropinirole, and rotigotine was validated as these dopamine agonists were thoroughly appraised for their efficacy and safety in clinical settings. In the context of PD, clinical benefits are evaluated in accordance with the unified PD rating scale (UPDRS), allowing a comprehensive and objective evaluation of the patient's condition. The UPDRS encompasses several aspects of PD patient's clinical status, notably mood and cognition, the ability to perform activities of daily life and motor performance, respectively evaluated using the section 1, 2 and 3 of the UPDRS scale (UPDRS 2 and 3) (Goetz et al., 2008). In clinical trials, drugs are evaluated according to what extent their administration is associated with the improvement of UPDRS scores when compared with placebo or a standard of care. Clinical studies performed on early PD patients proved pramipexole monotherapy to be more effective than placebo when considering the performance in daily life activities and motor performance (Hubble et al., 1995; Parkinson Study Group, 1997; Shannon, Bennett, & Friedman, 1997) while being more effective than pergolide only when assessing UPDRS 3 scores (Navan, Findley, Jeffs, Pearce, & Bain, 2003). Moreover, pramipexole was shown to induce dyskinesias and on-off fluctuations in a considerably lower proportion of patients when compared to L-DOPA after two and four years from the initiation of the therapy (Holloway et al., 2000). Similarly, pramipexole also showed its efficacy in improving motor performance and daily life activities when administered as adjunctive therapy to L-DOPA in later stages of the disease, with slight, but not significant superiority as compared to bromocriptine (Guttman, 1997; Lieberman, Ranhosky, & Korts, 1997; Mizuno et al., 2003; Pinter, Pogarell, & Oertel, 1999; Wermuth, 1998). Ropinirole was proven as an effective medication for the treatment of PD motor symptoms, significantly enhancing UPDRS 2 and 3 scores in both early- (Rascol et al., 2000; Stocchi et al., 2008), and late-stage (Pahwa et al., 2007; Stocchi, Giorgi, Hunter, & Schapira, 2011; Zhang et al., 2013) patients, respectively as a monotherapy or in combination with L-DOPA. Of note, it proved to be particularly efficient in delaying the occurrence of dyskinesia episodes in patients characterized by an unfavourable response to L-DOPA (Watts et al., 2010). Rotigotine, delivered as transdermal patch, proved its efficacy in alleviating the motor symptoms of PD (UPDRS 3) and in ameliorating the performance of daily life activity (UPDRS 2) as monotherapy in early-stage PD (Blindeauer, 2003; Giladi et al., 2007; Mizuno et al., 2013; Watts et al., 2007; Zhang et al., 2016) and as an adjuvant for L-DOPA therapy in late-stage PD (LeWitt, Lyons, & Pahwa, 2007; Nicholas et al., 2014; Zhang et al., 2017), maintaining a considerable long-term efficacy (Giladi, Boroojerdi, & Surmann, 2013).

2.2. Treatment of PD non-motor symptoms

Importantly, dopamine agonists were revealed as endowed with marked potential in tackling the non-motor symptoms associated with PD, such as depression, sleep disorder, or apathy, which are as much burdensome to patients as motor symptoms. Strikingly, pramipexole was scored superior to sertraline as a mood enhancer when measuring the depressive status of PD patients' according to the Hamilton Depression Rating Scale (HAM-D) (Barone et al., 2006). These initial findings were corroborated by further studies, positioning pramipexole as an efficient clinical tool for the management of PD-associated depression (Jiang, Jiang, Wang, & Li, 2021; Tundo, de Filippis, & de Crescenzo, 2019) and anhedonia (Lemke, Brecht, Koester, & Reichmann, 2006). Ropinirole showed to contribute as well at countering depression but has received greater attention for its capacity at improving sleep quality (Dušek et al., 2010; Rektorova et al., 2008). Such sleep-stabilizing feature has been also mentioned by patients receiving rotigotine, who in addition, experienced reduced

Table 1
Summary of the beneficial effects associated with the administration of non-ergot dopamine agonists to PD patients.

	Drug		
Beneficial Effect	*Pramipexole*	*Ropinirole*	*Rotigotine*
Enhancement of motor performance	✓	✓	✓
Antidepressant	✓	✓	–
Sleep stabilization	–	✓	✓

early-morning dystonia, likely due to the favourable pharmacokinetic properties of the transdermal patch formulation (Giladi, Fichtner, Poewe, & Boroojerdi, 2010; Trenkwalder et al., 2011). However, at variance with pramipexole and ropinirole, rotigotine failed to show significant efficacy against mood disorders (Raeder et al., 2021; Seppi et al., 2019). The beneficial effects of the prescription of pramipexole, ropinirole and rotigotine to PD patients are summarized in Table 1.

2.3. Adverse effects of non-ergot agonists

As previously mentioned, dopamine agonists have been successfully adopted in clinical settings as an efficient option to sometimes delay or more commonly to complement L-DOPA-based therapy to reduce the associated burdensome side effects. Nevertheless, the administration of pramipexole, ropinirole, and rotigotine is not entirely devoid of undesired consequences. Indeed, the prescription of these non-ergot dopamine agonists has been associated with the occurrence of motor complications such as dyskinesias and motor fluctuations (Ceravolo, Rossi, del Prete, & Bonuccelli, 2016). Nevertheless, these occur in a significantly limited proportion of cases when compared to L-DOPA (Giladi, Ghys, Surmann, Boroojerdi, & Jankovic, 2014; Hauser et al., 2007; Rascol et al., 2000; Thomas et al., 2006). This is likely attributed to the pharmacokinetic profile of dopamine agonists and especially rotigotine, delivered under the form of a transdermal patch, ensuring stable blood concentrations, at variance with L-DOPA. Moreover, the development of long-lasting drug delivery formulations for pramipexole and ropinirole ("extended-release" and "sustained release", respectively) offered a further amelioration of their pharmacokinetic profiles. These new formulations not only improved their tolerability (Pahwa et al., 2007; Schapira et al., 2011; Stocchi et al., 2011; Zhao et al., 2019) but also facilitated compliance by requiring single daily administration (Ceravolo et al., 2016).

Importantly, pramipexole (Biglan, Holloway, McDermott, & Richard, 2007; Holloway et al., 2000) and ropinirole (Rascol et al., 2000) have been associated with a significantly increased risk of inducing excessive daytime sleepiness (EDS) when compared to L-DOPA. EDS is considered as potentially dangerous since it can cause "sleep attacks", devoid of any prodromal sleepiness or fatigue, dramatically increasing the risk of car accidents (Ceravolo et al., 2016; Frucht, Rogers, Greene, Gordon, & Fahn, 1999; Hennessy et al., 2002). Of note, rotigotine was shown to improve sleep quality in patients by significantly reducing the incidence of EDS (Trenkwalder et al., 2011; Zhou, Zhang, Wang, & Peng, 2014). Another significantly relevant nervous adverse effect associated with dopamine agonists is the occurrence of impulse control disorders (ICDs), namely pathological gambling, hypersexuality, binge eating, compulsive buying, or punding (Ceravolo et al., 2016). The risk of developing ICD has been appraised as being significantly accrued when taking these two non-ergot dopamine agonists when compared to L-DOPA or rotigotine (Weintraub et al., 2010). Importantly, the frequency of ICDs is significantly increased in individuals with a personal history of substance use or familial history of psychiatric illnesses (Gatto & Aldinio, 2019), presenting an important confounding factor in the development of ICDs in PD patients treated with dopamine D_2-class receptor agonists. Of note, whereas no difference has been found in ICD incidence among patients treated with either pramipexole or ropinirole (13.4%), these side effects have been reported in a lower proportion (9%) of individuals treated with rotigotine (Frampton, 2019; Raeder et al., 2021). As such, rotigotine should be considered as the privileged dopamine agonist to be prescribed for patients at risk of developing ICDs (Raeder et al., 2021).

A relatively high proportion of PD patients experience psychotic episodes and hallucinations, mostly of visual nature, during the advanced stages of the disease (Schneider, Iourinets, & Richard, 2017). However, the incidence appeared generally increased with antiparkinsonian drugs, notably the dopamine agonists pramipexole and ropinirole (Pérez-Pérez et al., 2015; Zhao et al., 2019), while rotigotine was associated with hallucinations in a more limited group of patients (5%) (Frampton, 2019). Requiring the introduction of antipsychotics, the clinical management of these drug-induced increase in hallucinatory phenomena poses a significant challenge in the context of treating PD patients' motor symptoms. Indeed, due to their antagonist profile at the D_2 receptor, antipsychotics may substantially hinder motor performances. Thus, the prescription of atypical antipsychotics, endowed with a reduced impact on locomotion, is preferred. In this context, clozapine was shown to limit psychotic episodes without exerting any influence on UPDRS 3 scores (Factor, Friedman, Lannon, Oakes, & Bourgeois, 2001). Nevertheless, prescribing clozapine exposes patients to the risk of developing agranulocytosis, requiring a regular control of white cell counts (Hack et al., 2014). At the moment, tackling hallucinations and psychosis related to PD and its medication with other atypical antipsychotics such as risperidone, quetiapine, olanzapine or aripiprazole remains a matter of debate and has been regarded as counterproductive with respect to motor performance (Kyle & Bronstein, 2020; Weintraub, Chen, Ignacio, Mamikonyan, & Kales, 2011; Zhang et al., 2019).

Of note, recent clinical trials involving the antipsychotic compound pimavanserin have indicated this drug as an effective and tolerable option for the treatment of psychotic symptoms in PD patients, leading to its recent approval and clinical use specifically in this context (Friedman, 2013; Zhang et al., 2019). Such a beneficial profile is likely to be associated with the inverse agonism at the hallucinogen-activated serotonin $5HT_{2A}$ receptor, together with a lack of affinity for the dopamine D_2 receptor (Friedman, 2013; Vanover et al., 2006). Of note, dopamine agonists also cause peripheral side effects related to the stimulation of dopamine receptors located outside the central nervous system. Symptoms can be mild and disappear after the first weeks of treatment with the development of tolerance, but are still susceptible to reduce patient compliance (Ceravolo et al., 2016). Peripheral side effects such as nausea, vomiting, and oedema can be avoided by switching from pramipexole or ropinirole to rotigotine (Oertel et al., 2013; Woitalla et al., 2015). However, 46% of patients receiving rotigotine transdermal patches have reported mild skin reactions following patch application (Reichmann, 2009). Importantly, the cardiac side effects associated with ergot-derived dopamine agonists such as bromocriptine, cabergoline, or pergolide are not observed with pramipexole, ropinirole, and rotigotine, which are devoid of any activity at the serotonin $5HT_{2B}$ receptor, limiting the risk of fibrotic heart reactions (Ceravolo et al., 2016). Nevertheless, non-ergot compounds have been associated with an increased incidence of orthostatic hypotension (Ceravolo et al., 2016; Zhuo et al., 2017), while the risk of heart failures has been reported to be increased only with pramipexole (Mokhles et al., 2012). Even though dopamine agonists are not devoid of side effects, they are commonly well-tolerated and efficient at treating motor symptoms. Hence, discontinuing dopamine agonist treatment upon observation of adverse effects can result in neurological complications grouped under the name of dopamine agonist withdrawal syndrome. This condition - which includes anxiety, panic, phobias, and irritability - is not reversed by L-DOPA administration, and may present a challenge for the clinical long-term handling of patients (Yu & Fernandez, 2017). The adverse effects observed as a consequence of the prescription of pramipexole, ropinirole and rotigotine to PD patients are summarized in Table 2.

Table 2
Summary of the undesired effects associated with the administration of non-ergot dopamine agonists to PD patients.

	Drug		
Undesired Effect	*Pramipexole*	*Ropinirole*	*Rotigotine*
Dyskinesias	✓	✓	–
Early morning offs / Motor fluctuations	✓	✓	–
ICDs	✓	✓	–
Hallucinations	✓	✓	–
EDS	✓	✓	–
Heart failure	✓	–	–
Orthostatic hypotension	✓	✓	✓
Fibrotic reactions	–	–	–
Nausea/vomiting	✓	✓	–
Oedema	✓	✓	–
Skin reactions	–	–	✓

2.4. Comparison of the clinical effectiveness of pramipexole, ropinirole, and rotigotine

Overall, pramipexole, ropinirole and rotigotine have been recognized as effective at treating both motor symptoms and non-motor symptoms and are generally associated with a favourable degree of tolerability. However, beyond their rather common clinical profile, underscoring the distinctive features of these compounds is of importance in the context of therapeutic optimization. A meta-analysis comparing the long-lasting formulations of pramipexole and ropinirole as adjunct therapies in late-PD have designated ropinirole as superior to pramipexole when considering the improvement of daily activities performance measured by the UPDRS 2 scale while being more likely than pramipexole to induce somnolence, and without significant difference in UPDRS 3 score and the incidence of other adverse effects (Zhao et al., 2019). A comprehensive meta-analysis (Binde, Tvete, Gåsemyr, Natvig, & Klemp, 2020) comparing all the pharmacological treatments for PD (including dopamine agonists, L-DOPA, and MAO-B inhibitors) pointed at ropinirole as the most efficient monotherapeutic option when treating early PD motor symptoms, followed by L-DOPA. In this ranking, pramipexole and rotigotine showed comparable efficacy, inferior to L-DOPA but higher than ergot agonists and MAO-B inhibitors. Nevertheless, when considering the same scale for adjunct therapies to L-DOPA in later PD stages, selegiline appeared as the highest-ranking drug, with pramipexole, ropinirole, and rotigotine characterized by comparable scores. Pramipexole was reported as the dopamine agonist associated with the highest risk of developing adverse effects. Finally, the study concluded that dopamine agonists are effective, globally well-tolerated, and capable of reducing the frequency of therapy discontinuation when used as an adjunct to L-DOPA therapies. These conclusions are consistent with another previously published meta-analysis, pointing at ropinirole and pramipexole as the most effective dopamine agonists, while considering rotigotine slightly less effective at treating motor symptoms, but endowed with greater effectiveness at treating non-motor symptoms and with improved tolerability, especially when compared to pramipexole (Zhuo et al., 2017). Hence, when considering global UPDRS and withdrawal scores, rotigotine and ropinirole are considered as the optimal therapeutic options (Zhuo et al., 2017).

The outcomes of distinct clinical trials may differ due to the nature of the demographics of the selected cohorts, the study design, dosages, and protocols. Nevertheless, the vast majority of the available clinical evidence describes pramipexole, ropinirole, and rotigotine as effective compounds for the treatment of motor and non-motor symptoms in both early and late PD, as monotherapy and adjunct therapy to L-DOPA, respectively. Albeit adverse effects have been reported, their occurrence and intensity remain relatively limited. As such, the risks of prescribing pramipexole, ropinirole, or rotigotine seem to be largely outweighed by the benefits of these compounds on patients' quality of life. However, the identification of the distinct assets of each compound may present the rationale for evidence-based therapeutic adaptation and optimization, with increased beneficial potential for both clinicians and patients. In detail, the cited studies enable to speculate that patients experiencing severe motor impairment may find ropinirole as the most effective therapeutic choice among the three herein considered dopamine agonists.

Table 3
Outline of the recommended first-choice dopamine agonists to be administered to PD patients according to their clinical profile.

Clinical manifestation	Origin	Recommended dopamine agonist
Severe motor impairment	*PD*	Ropinirole, Pramipexole (Rotigotine)
Depression, anhedonia		Ropinirole, Pramipexole
Impaired sleep		Rotigotine
History of cardiovascular pathologies	*Patient-specific genetics, familial history or pre-existing conditions*	Rotigotine (Ropinirole)
Familial or personal history of psychiatric disturbances		Rotigotine
Psychosis, hallucination, ICDs, Dyskinesias, early-morning off, motor complications	*Previous treatment with dopamine agonists (Pramipexole, Ropinirole)*	Rotigotine Rotigotine
Nausea, vomiting, oedema		Rotigotine

Ropinirole and pramipexole may also be privileged in the context of patients with depressive manifestations or anhedonia, while pramipexole shall be avoided in patients vulnerable to cardiovascular diseases. Rotigotine presents the most tolerable profile among the examined drugs and may thus prove beneficial in patients requiring sleep quality improvements and are thus at risk of EDS, together with limited risks of psychiatric side effects in patients with a familial history of psychiatric disorder or a personal history of gambling or reward-seeking behaviour. Indeed, switching to rotigotine appears as ideal for patients treated with other dopamine agonists reporting hallucinations or ICDs, but also motor complications such as early morning offs. In conclusion, the detailed appraise of the currently available literature, together with further clinical research regarding the non-ergot dopamine agonists pramipexole, ropinirole and rotigotine may provide fruitful insights for the effective personalization of antiparkinsonian therapy. Indeed, the fine-grained distinctive features of the considered drugs call for a careful, patient-tailored approach that might present potential opportunities for the effective treatment of PD. The hereby described clinical evidence is recapitulated in Table 3, outlining the current literature supporting for the prescription of pramipexole, ropinirole, and rotigotine as a function of the clinical profiles presented by PD patients.

3. Putative implications of the binding profiles of pramipexole, ropinirole, and rotigotine

The affinity of pramipexole, ropinirole, or rotigotine for the five dopamine receptor subtypes has been estimated from in vitro binding studies. As summarized in Table 4, competitions experiments were conducted with reference radioligands on models of cultured cells recombinantly expressing the human sequences encoding these receptors. The affinity profiles for the three compounds are graphically illustrated in Fig. 2. Such methodology enables to appreciate the preferential binding of pramipexole for the D_3 receptor (Mierau et al., 1995; Millan et al., 2002; Perachon, Schwartz, & Sokoloff, 1999) (Table 4). Millan et al. also showed that pramipexole binds the D_4 receptor with an affinity in the 10 nM range, intermediate between the D_2 and D_3 receptors (Millan et al., 2002). Plus, pramipexole appeared to present some binding preference for the D_{2S} (pKi= 6.02) as compared to the D_{2L} receptor (pKi= 5.77) (Millan et al., 2002). Importantly, in all the

Table 4
Summary of the currently available literature on competition binding studies performed on recombinant cell lines aiming to evaluate the affinity of pramipexole, ropinirole, and rotigotine for all the human dopamine receptor subtypes. Affinities are expressed as Ki (nM). For every cited study, the experimental model and radioligand are presented. Since the vast majority of the gathered studies did not distinguish between D_{2L} or D_{2S} receptors, the depicted data only refer to D_2 receptors, without differentiating the affinity of the studied compounds for the two splice variants. N/A; Not Applicable, as the authors could not measure any displacement of the radioligand.

	D_1 receptor			
	Ki (nM)	Radioligand	Experimental model	Reference
Pramipexole	N/A	[^{3}H] SCH23390	LMtk mouse fibroblasts	(Wood et al., 2015)
	N/A	[^{3}H] SCH23390	CHO cells	(Perachon et al., 1999)
	N/A	[^{3}H] SCH23390	CHO cells	(Millan et al., 2002)
Ropinirole	N/A	[^{3}H] SCH23390	LMtk mouse fibroblasts	(Wood et al., 2015)
	N/A	[^{3}H] SCH23390	CHO cells	(Perachon et al., 1999)
	N/A	[^{3}H] SCH23390	CHO cells	(Millan et al., 2002)
Rotigotine	83.00	[^{3}H] SCH23390	CHO cells	(Scheller et al., 2009)
	251.19	[^{3}H] SCH23390	LMtk mouse fibroblasts	(Wood et al., 2015)
	D_2 receptor			
	Ki (nM)	Radioligand	Experimental model	Reference
Pramipexole	2.07	[^{3}H] Spiperone	HEK293 cells	(Mierau et al., 1995)
	199.53	[^{3}H] Spiperone	CHO cells	(Wood et al., 2015)
	616.00	[^{125}I] Iodosulpiride	CHO cells	(Perachon et al., 1999)
	1698.24	[^{125}I] Iodosulpiride	CHO cells	(Millan et al., 2002)
Ropinirole	29.00	[^{3}H] Spiperone	Human striatum	(Eden et al., 1991)
	398.11	[^{3}H] Spiperone	CHO cells	(Wood et al., 2015)
	970.00	[^{125}I] Iodosulpiride	CHO cells	(Perachon et al., 1999)
	933.25	[^{125}I] Iodosulpiride	CHO cells	(Millan et al., 2002)
Rotigotine	17.00	[^{3}H] Butaclamol	CHO cells	(Scheller et al., 2009)
	2.00	[^{3}H] Spiperone	CHO cells	(Wood et al., 2015)
	D_3 receptor			
	Ki (nM)	Radioligand	Experimental Model	Reference
Pramipexole	0.49	[^{3}H] Spiperone	CHO cells	(Mierau et al., 1995)
	0.25	[^{3}H] Raclopride	CHO cells	(Wood et al., 2015)
	8.50	[^{125}I] Iodosulpiride	CHO cells	(Perachon et al., 1999)
	10.47	[^{125}I] Iodosulpiride	CHO cells	(Millan et al., 2002)
Ropinirole	10.00	[^{3}H] Raclopride	CHO cells	(Wood et al., 2015)
	61.00	[^{125}I] Iodosulpiride	CHO cells	(Perachon et al., 1999)
	37.15	[^{125}I] Iodosulpiride	CHO cells	(Millan et al., 2002)
Rotigotine	0.71	[^{3}H] Butaclamol	SH-SY5Y cells	(Scheller et al., 2009)
	0.10	[^{3}H] Raclopride	CHO cells	(Wood et al., 2015)
	D_4 receptor			
	Ki (nM)	Radioligand	Experimental Model	Reference
Pramipexole	2.76	[^{3}H] Spiperone	CHO cells	(Mierau et al., 1995)
	63.10	[^{3}H] Spiperone	CHO cells	(Wood et al., 2015)
	128.82	[^{3}H] Spiperone	CHO cells	(Millan et al., 2002)
Ropinirole	251.19	[^{3}H] Spiperone	CHO cells	(Wood et al., 2015)
	851.14	[^{3}H] Spiperone	CHO cells	(Millan et al., 2002)
Rotigotine	15.00	[^{3}H] Clozapine	CHO cells	(Scheller et al., 2009)
	19.95	[^{3}H] Spiperone	CHO cells	(Wood et al., 2015)
	D_5 receptor			
	Ki (nM)	Radioligand	Experimental Model	Reference
Pramipexole	N/A	[^{3}H] SCH23390	Chem-1 cells	(Wood et al., 2015)
	N/A	[^{3}H] SCH23390	CHO cells	(Millan et al., 2002)
Ropinirole	N/A	[^{3}H] SCH23390	Chem-1 cells	(Wood et al., 2015)
	N/A	[^{3}H] SCH23390	CHO cells	(Millan et al., 2002)
Rotigotine	6,30	[^{3}H] SCH23390	CHO cells	(Scheller et al., 2009)
	39.81	[^{3}H] SCH23390	Chem-1 cells	(Wood et al., 2015)

cited reports, pramipexole displayed no relevant affinity for neither the D_1 nor the D_5 receptor. Thus, the binding profile of pramipexole at dopamine receptors can be summarized by the ranking order $D_3 > D_4 > D_{2S} > D_{2L}$. Ropinirole showed a binding profile comparable to pramipexole, demonstrating a high affinity for D_3, D_4, and D_2 receptors and displaying no relevant affinity for the members of the D_1-class receptor family (Millan et al., 2002; Perachon et al., 1999; Wood, Dubois, Scheller, & Gillard, 2015). In addition, its highest affinity was displayed for the D_3 receptor, but, at variance with pramipexole, ropinirole recognized the D_2 receptor isoforms (pKi = 6.17 at D_{2S} and pKi = 6.03 at D_{2L}) and the D_4 receptors (pKi = 6.07) with similar affinities. The binding ranking order of ropinirole is outlined as being $D_3 > D_{2S}=D_4=D_{2L}$. Of note, pramipexole and ropinirole shared limited affinity for non-dopaminergic receptors such as the adrenergic receptors α_{2a} and α_{2b}, the serotonin receptors $5HT_{1A}$ and $5HT_{1D}$, and the histamine receptor H_1 (Millan et al., 2002).

While ropinirole appeared somewhat less selective for the D_3 receptor when compared to pramipexole, the binding profiles of both dopamine agonists at the different dopamine receptors appeared similar. They share a marked selectivity for members of the D_2 receptor family, which may explain the marked influence on locomotor behaviour reported in animal studies (Eden et al., 1991; Mierau & Schingnitz, 1992) and the favourable outcome in clinical studies. Indeed, binding at members of the D_2 receptor family likely

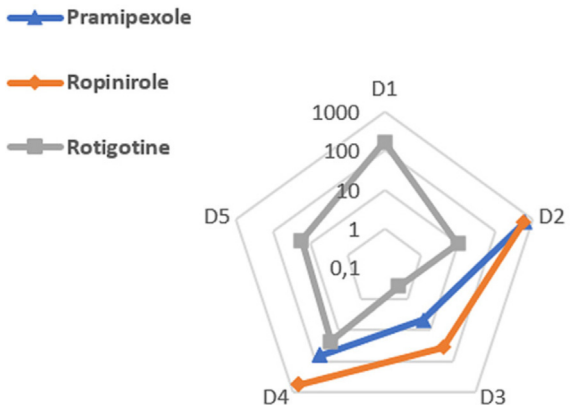

Fig. 2. Radar plot summarizing the binding affinities (average Ki values in nM) of pramipexole, ropinirole, and rotigotinefor the different dopamine receptor subtypes. This figure summarizes the data represented in Table 4.

underpins their efficacy at treating motor symptoms, while limited interaction with members of the D_1 receptor family, preclude the risk of inducing dyskinesias (Aubert et al., 2005; Feyder, Bonito-Oliva, & Fisone, 2011; Jones-Tabah et al., 2020). At the same time, a high affinity for D_3 receptors is regarded as especially favourable for the pharmacological handling of PD-associated psychiatric symptoms, notably the treatment of motivational deficits (Carnicella et al., 2014). Also, compounds characterized by preferential D_2 receptor affinity are also reported as possessing anti-depressant activities (Basso et al., 2005; Breuer et al., 2009; Carnicella et al., 2014). Indeed, the combined D_3/D_2 binding profile of ropinirole and pramipexole might provide a molecular explanation for the non-motor benefits reported in clinical trials (Jiang et al., 2021; Rektorova et al., 2008). Besides, the D_3 selectivity has also been shown to limit LIDs (Riddle et al., 2011) and to promote the activation of neuroprotective signalling pathways (Beom, Cheong, Torres, Caron, & Kim, 2004; Collo, Zanetti, Missale, & Spano, 2008). These observations have been corroborated by clinical investigations underscoring the reduced prevalence of dyskinesias in PD patients treated with D_3-specific dopamine agonists instead of L-DOPA (Chondrogiorgi, Tatsioni, Reichmann, & Konitsiotis, 2014). Worth noting is the relevant affinity of both pramipexole and ropinirole for the D_4 receptors. In the light of evidence for the role of this receptor subtype in the dopamine mediated control of emotion processing, reviewed by Lauzon and Laviolette (Lauzon & Laviolette, 2010), the D_4 receptor activation might play a role in the occurrence of ICDs reported in PD patients receiving pramipexole and ropinirole.

Together, all these in vitro binding studies have provided rational evidence to distinguish pramipexole and ropinirole from ergot-derived dopamine agonists such as pergolide, lisuride, and bromocriptine, all characterized by a mixed D_1 and D_2 receptors binding profile. At variance, rotigotine shows a rather peculiar profile, characterized by a broad-spectrum binding profile comparable to earlier developed ergot-derived dopamine agonists. With a subnanomolar affinity for the D_3 receptor, a nanomolar affinity for D_4, D_5, and D_2 receptors, and lower (pKi= 7.08 nM) but physiologically and clinically relevant affinity for D_1 receptors (Scheller, Ullmer, Berkels, Gwarek, & Lübbert, 2009), the binding profile of rotigotine is thus $D_3 > D_5 > D_2$–D_4, D_1 (Scheller et al., 2009; Wood et al., 2015). Of note, kinetic studies indicated rotigotine as a slow dissociating ligand from D_2 and D_3 receptors when compared to other dopamine receptor subtypes (Wood et al., 2015). With its 10-fold higher affinity for the D_3 receptor as compared to the D_2 receptor, rotigotine behaves as a D_3-preferring agonist, like pramipexole and ropinirole. The comparison of these three non-ergot dopamine agonists reveals rotigotine as presenting the highest affinity for both the D_3 and D_2 receptors (Table 4, Fig. 2), but nevertheless interacting with all dopamine receptors at the clinically relevant concentration of 2.5 nM (Poewe & Leussi, 2005). Rotigotine also displayed nanomolar affinity for the adrenergic α_{2B} and serotonin $5HT_{1B}$ receptors (Scheller et al., 2009).

Considering that the concomitant activation of D_1 and D_2 receptors has been associated with synergistic responses in experimental models of PD, the modest but clinically relevant activity of rotigotine at the D_1 receptor was proposed to explain its beneficial effect in treating PD motor symptoms (Robertson, 1992; Vermeulen et al., 1994; Vermeulen, Drukarch, Wolters, & Stoof, 1999). Nevertheless, albeit indicating its superior tolerability, meta-analyses comparing rotigotine to pramipexole or ropinirole (both lacking affinity for D_1 receptors) did not position rotigotine as the most effective dopamine agonist for the treatment of PD (Binde et al., 2020; Zhuo et al., 2017). Thus, the binding of rotigotine to D_1 receptors could possibly contribute to tackle cognition deficits in PD patients, while providing marginal - or even negligible - locomotor benefits. In this context, it is interesting to note that pramipexole and ropinirole, showing prominent selectivity at D_2 -class receptors, have been associated with a higher risk of causing ICDs and EDS when compared to other dopamine receptor ligands, including rotigotine (Ceravolo et al., 2016; Frampton, 2019; Moore, Glenmullen, & Mattison, 2014; Raeder et al., 2021; Weintraub et al., 2010; Zhou et al., 2014). However, the selective D_3/D_2 binding profile of these agonists has been associated with antidepressant properties, which are absent in rotigotine, despite being associated with a high affinity and a slow dissociation kinetic in regards of these dopamine receptor subtypes (Raeder et al., 2021; Rektorova et al., 2008; Tundo et al., 2019). Overall, the broad binding profile of rotigotine for dopamine receptors is accompanied by the limited occurrence of motor and non-motor undesired effects (Wood et al., 2015), together with a slightly reduced efficacy at treating motor symptoms and PD-associated depression when compared to ropinirole and pramipexole. As such, the pharmacology of rotigotine appears complex and somehow enigmatic, deserving further investigation. Indeed, a deeper exploration of the pharmacodynamic properties of rotigotine might unravel the molecular determinants of its particularly appreciate clinical outcomes and pave the way for the design of the next generation of dopamine agonists. Of importance, the hereby presented analysis overlooks the affinity that the considered compounds have for non-dopaminergic receptors, namely adrenaline and serotonin receptors (Millan et al., 2002). Hence, we cannot exclude that the thorough analysis of the non-dopaminergic components of these ligands essentially classified as dopamine agonists may contribute at reconciling the discrepancies between their affinities at dopamine receptors and clinical observations.

It is essential to figure out that the analysis of receptor binding profiles may not be sufficient to explain or predict the clinical properties of dopamine receptor ligands considered for the treatment of PD. Indeed, binding studies exclusively reveal the affinity, but not the functional properties of the examined compounds at dopamine receptors and their downstream consequences, which are mediated by a large variety of intracellular signalling partners. Therefore, a deeper characterization of the pharmacological properties of non-ergot dopamine ligands requires the study of dopamine receptor signalling triggered by these compounds. Noteworthy, the signalling associated with every receptor subtype is endowed with remarkable complexity. However, given the pivotal role of the dopamine D_2 receptor in motor control, together with its recognized role as a key therapeutic target in PD (further supported by the fact that the D_2 receptor is recognized by all clinically used dopamine agonists), the scope of this review is purposely narrowed to the signalling properties at the D_2 receptor only.

4. Dopamine D_2 receptor signalling

Reinforcing the deficient dopaminergic transmission in the dorsal striatum is the essential objective of the pharmacological treatments of PD. The administration of dopamine agonists to substitute for

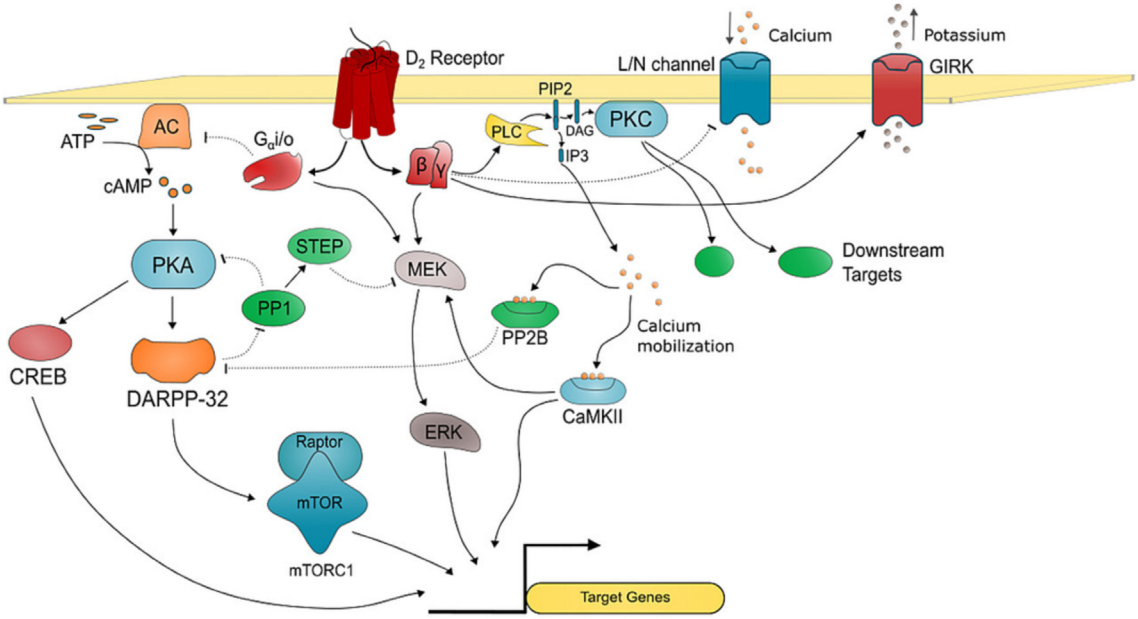

Fig. 3. G protein-dependent signalling evoked by D_2 receptors. Arrows indicate an activating action, whereas t-shaped dotted lines indicate an inhibitory effect. Abbreviations : AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; DAG, diacylglycerol; DARPP-32, dopamine- and cAMP-regulated neuronal phosphoprotein; ERK, extracellular signal-regulated kinase; IP_3, inositol trisphosphate; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; PP1, protein phosphatase 1; PP2B, protein phosphatase 2B; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; STEP, striatal-enriched protein-tyrosine phosphatase.

dopamine appears as a rational option, but a deep knowledge of the cellular responses associated with dopamine receptors is of critical importance for the development of optimized treatments. Dopamine receptors transduce signals through their coupling with heterotrimeric guanine nucleotide-binding proteins (G proteins which contains the three subunits, recognized as α, β and γ), that modulate intracellular biochemical cascades influencing the activity of responding neurons. In the striatum, dopamine-related behavioural and locomotor manifestations do not exclusively depend on G proteins, but also on arrestins which operate as scaffolding proteins best known for their role in G protein uncoupling, receptor desensitization and internalization. Arrestins are also recognized as complementary signalling partners for which a major role has been revealed in the context of dopamine-mediated controls of behaviour and locomotion (Beaulieu & Gainetdinov, 2011; Smith, Lefkowitz, & Rajagopal, 2018).

4.1. G protein signalling at the D_2 receptor

Dopamine D_2 receptors mediate their influence on cell signals mainly through a preferential coupling with pertussis toxin-sensitive Gi/o proteins, which, by inhibiting the activity of adenylate cyclase, reduce the production of cyclic AMP (cAMP) with a variety of influences on cell activities. Best documented is the inhibitory effect on the cAMP/protein kinase A/dopamine- and cAMP-regulated phosphoprotein (cAMP/PKA/DARPP-32) cascade. The inhibition of the activity of DARPP-32 leads to several downstream outcomes, including the increase in the activity of phosphatase 1 (PP1), which counters PKA-induced phosphorylation on its substrates. Among these, the cAMP response element-binding protein (CREB) regulates a variety of gene expression programs related to synaptic plasticity. Moreover, the increased activity of PP1 promotes the activation of striatal-enriched protein-tyrosine phosphatase (STEP), a phosphatase responsible for the inhibition of the mitogen-activated protein kinase kinase (MEK), the upstream kinase activating extracellular signal-regulated kinases (ERK) (Beaulieu & Gainetdinov, 2011). This biochemical cascade, together with the modulation of the activity of the mammalian target of rapamycin complex 1 (mTORC1), contributes to the regulation of gene expression mediated by Gi/o proteins recruited at the activated D_2 receptor (Fig. 3) (Oh, Chartisathian, Ahmed, & Chase, 2003; Santini et al., 2007, 2012; Santini, Heiman, Greengard, Valjent, & Fisone, 2009).

Importantly, experiments performed on a bacterial artificial chromosome transgenic mouse model proved that the inhibition of the cAMP/PKA/DARPP-32 pathway is responsible for the modulation of basal and drug-induced locomotion (Bateup et al., 2008). In the central nervous system, D_2 receptors mainly influence the activity of these effectors through the coupling with Go proteins, rather than Gi (Jiang, Spicher, Boulay, Wang, & Birnbaumer, 2001). Besides the role of the α subunit, the βγ subunit heterodimer of the G proteins were also assigned with relevant signalling properties in the case of D_2 receptor. After the dissociation from the heterotrimeric G protein, the βγ heterodimer interacts with G protein-coupled inwardly-rectifying potassium channels (GIRKs), causing potassium efflux and membrane hyperpolarization (Kuzhikandathil, Yu, & Oxford, 1998; Lavine et al., 2002) (Fig. 3). Moreover, the βγ complex tightly regulates intracellular signalling by activating phospholipase C-mediated PKC activation and cellular calcium mobilization together with inhibiting the activity of L-type and N-type voltage-activated calcium channels (Hernández-López et al., 2000; Yan, Song, & Surmeier, 1997) (Fig. 3). The consequent oscillations in calcium concentration promote the activation of Ca2+/calmodulin-dependent protein kinase II (CaMKII) (Takeuchi, Fukunaga, & Miyamoto, 2002), and of the serine/threonine-protein phosphatase 2B (PP2B) (Bateup et al., 2008) - also referred to as calcineurin - mediating the cAMP-independent inhibition of DARPP-32 (Nishi, Snyder, & Greengard, 1997) (Fig. 3). Of note, the activation of the mitogen-activated protein kinase (MAPK) cascade (including MEK and ERK) in response to D_2 receptor stimulation appears to be mediated by both Go and Gβγ subunits (Jin et al., 2013; Neve, Seamans, & Trantham-Davidson, 2004).

4.2. Arrestin signalling at the D_2 receptor

The stimulation of GPCRs is followed by the recruitment of GPCR kinases (GRKs), a family of enzymes that phosphorylate a specific subset of serine and threonine residues in the third intracellular loop and

C-terminus of the activated receptor (Smith & Rajagopal, 2016). This phenomenon promotes the interaction of arrestins with the phosphorylated receptor, which in turn sterically interferes with the G protein recruitment, resulting in signal extinction and subsequent receptor desensitization. Moreover, arrestins are able to recruit clathrin and AP2 proteins, triggering the receptor internalization process (Lefkowitz & Shenoy, 2005). Beside this well documented implication in the agonist-induced receptor regulation, arrestins, and especially the ubiquitously expressed non-visual arrestin isoforms βarrestin1 and βarrestin2, have received remarkable attention for their signalling properties. This process has long been described as strictly independent from G proteins and appears to be mediated by the scaffolding of signalling partners, notably kinases and their targets (Lefkowitz & Shenoy, 2005). The role of βarrestin2 as essential GPCR signalling partners has been documented for several GPCRs, including the dopamine D_2 receptor (Smith & Rajagopal, 2016).

In vitro studies aimed at deciphering the properties of the βarrestin2-mediated signalling at the stimulated D_2 receptor highlighted a distinct kinetic when compared to G protein signalling. Notably, the onset of ERK1/2 phosphorylation as a consequence of G protein-mediated activation of the cAMP/PKA/DARPP32 pathway activation was reported as rapidly peaking and then fading after 30 minutes (Svenningsson et al., 2003; Valjent et al., 2000, 2005). At variance, arrestin-mediated protein kinase B (PKB) inhibition could not be detected within 30 minutes from receptor stimulation, but lasted for a prolonged duration (estimated around 2 hours) and was not subjected to desensitization (Ahn, Shenoy, Wei, & Lefkowitz, 2004; Beaulieu et al., 2004, 2005). As such, βarrestin2 recruitment was associated with the termination of the early-phase component of signal transmission and the subsequent induction of a late-phase, longer-lasting signalling. This bimodal kinetic would allow neurons to establish distinct degrees of responsiveness to dopamine transmission, favouring the integration of the signal with both immediate- and late effects (Beaulieu & Gainetdinov, 2011).

In vivo, the pivotal role of βarrestin2 in dopaminergic neurotransmission has been highlighted after observing that the ablation of the gene encoding for βarrestin2 in transgenic mice led to a significant reduction in amphetamine- or apomorphine-induced locomotion. Further studies on transgenic mice highlighted that such effects are dependent on the phosphorylation of the D_2 receptors by GRK6, and the consequent recruitment of βarrestin2, which in turn promotes the interactions between the protein phosphatase 2A (PP2A) and PKB enzymes (Beaulieu et al., 2005; Gainetdinov et al., 2003) (Fig. 4). As such, the activity of PKB will be inhibited by the PP2A-mediated dephosphorylation, promoting the action of glycogen synthase kinase 3 beta (GSK3β). Convincingly, both the pharmacological inhibition or the genetic ablation of GSK3β in mice cause a drastic reduction in basal and dopaminergic drug-induced locomotion. This hypolocomotor phenotype is strictly comparable to the one observed in transgenic mice invalidated for the βarrestin2 gene, positioning GSK3β as a pivotal actor in dopamine neurobiology (Beaulieu et al., 2004, 2005). In detail, GSK3β exerts its downstream effects on motor behaviour by interfering with the excitatory glutamate transmission in D_2 receptors-expressing MSNs. The activation of GSK3β enzyme has been indicated as promoting long term depression in rats (Peineau et al., 2007, 2008), reducing the function and transcription of NMDA receptor subunits (Chen, Gu, Liu, & Yan, 2007; Li, Xi, Roman, Huang, & Gao, 2009; Zhu et al., 2007) and hampering the membrane translocation of AMPA receptors (Du et al., 2010) (Fig. 4). By reducing the presence of these ionotropic glutamate receptors at the cell membrane of MSNs, the activation of GSK3β leads D_2 receptor-expressing neurons to become less responsive to the excitatory glutamate transmission. Given their gatekeeper role of the inhibitory, indirect pathway of motor control, the lack of glutamate-induced neuron depolarization facilitates the initiation of of motor programs. Indeed, optogenetic studies revealed that the selective depolarization of D_2-expressing MSNs reduces locomotion (Kravitz et al., 2010). Of note, the capacity of D_2 receptor-derived mediated βarrestin2

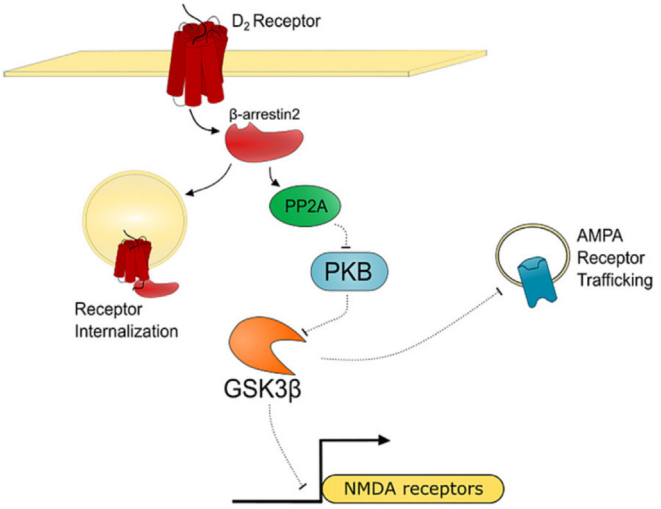

Fig. 4. Arrestin-mediated signalling downstream of the activation of the D_2 receptor. Arrows indicate an activating action, whereas t-shaped dotted lines indicate an inhibitory effect. Abbreviations: AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GSK3β, glycogen synthase kinase 3 beta; NMDA; N-methyl-D-aspartate, PP2A, protein phosphatase 2A; PKB, protein kinase B.

signalling to activate ERK has been subject to debate (Beom et al., 2004). However, currently accepted biochemical evidence have proven that Gi/o proteins are required for the activation of ERK in response to D_2 receptor stimulation (Jin et al., 2013; Quan, Kim, Albert, Choi, & Kim, 2008).

Taken together, the evidence for a multimodal signalling transmission in response to dopamine D_2 receptor activation is extensive and robust. Moreover, the thorough analysis of dopamine receptor signalling by diverse agonist has highlighted a relevant degree of complexity, in line with the roles of dopamine in mediating both cognitive and locomotor behaviour. Importantly, the wealth and differentiation of dopamine receptor signalling might be harnessed by a subset of receptor ligands capable of orienting the coupling of the GPCRs in distinct fashions to obtain enhanced pharmacological profiles endowed with promising therapeutic perspectives.

4.3. Ligand bias at the D_2 receptor in PD

As indicated here above, GPCRs are endowed with the capacity to trigger distinct downstream signalling not only through multiple G proteins but also through the recruitment of arrestins. This multimodal signalling has opened therapeutic avenues of great interest, as the extensive examination of the distinct signalling profiles of synthetic ligands has determined the existence of compounds capable of preferentially activating one signalling pathway over another. This property, referred to as "ligand bias" or "functional selectivity", has opened the possibility to develop pharmacological agents capable of targeting beneficial signal pathways while potentially avoiding the occurrence of undesirable effects. As such, functionally selective drugs might be characterized by an enhanced clinical profile in terms of tolerability when compared to compounds that would indiscriminately trigger the signalling pathways associated with receptor activation, which are referred to as unbiased or balanced ligands (Kenakin, 2013, 2019; Whalen, Rajagopal, & Lefkowitz, 2011) (Fig. 5). In this context, the detailed understanding of the physio-pathological implication of the G protein and βarrestin2 signalling cascades in response to dopamine D_2 receptor activation is required to appreciate the relevance and therapeutic potential of biased dopamine receptor ligands in the pharmacological treatment of PD.

The observations obtained from the thorough experiments published by Beaulieu et al. have enabled to identify βarrestin2 as a

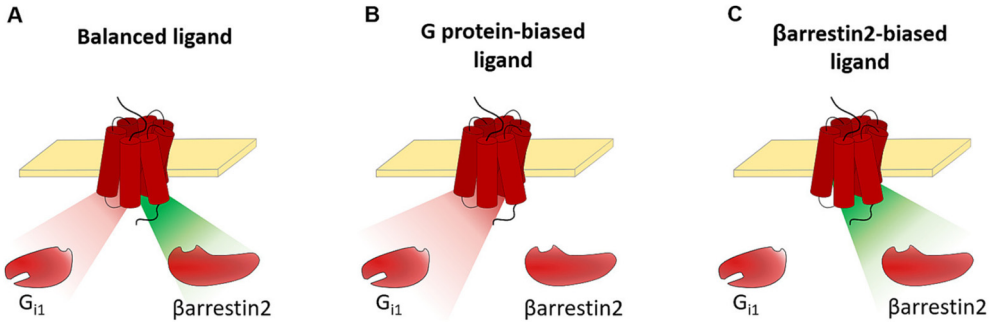

Fig. 5. Graphical representation of the concept of functional selectivity. Balanced ligands (A) recruit both G proteins and arrestins with similar efficiencies (indicated by shaded areas of similar proportions). G protein- biased ligands (B) preferentially recruit G proteins over arrestins, while arrestin-biased ligands preferentially recruit arrestins over G proteins (indicated by shaded areas of different proportions).

key mediator of D2 receptor-mediated modulation of locomotion, providing a strong rationale for supporting βarrestin2-biased ligands as putatively beneficial in PD treatments (Beaulieu et al., 2004, 2005, 2007, b, 2015). These findings were corroborated by reports describing the rescuing of the hypolocomotor phenotype of transgenic mice invalidated for the D2 receptor gene through the viral expression of a mutant D2 receptor capable of signalling exclusively through βarrestin2 in the indirect pathway MSNs (Donthamsetti et al., 2020). Comparing the behavioural effect of G protein-biased and βarrestin2-biased mutant D2 receptors using the same viral reconstitution approach highlighted that both signal transducers are required to fully recapitulate amphetamine-induced locomotion (Rose et al., 2018). As such, both βarrestin2 and G protein signalling participate in concert but with distinct relative impact to the establishment of D2-induced locomotion. Of note, while cocaine-induced motor behaviour was comparably rescued by both mutant receptors, the motor effects triggered by phencyclidine (a glutamate antagonist, inducing psychosis-like cognitive impairment) appeared dependent on the sole action of βarrestin2, adding a further layer of complexity to the pharmacology of biased dopaminergic signalling (Rose et al., 2018). Taken together, these research works point to D2 receptor-related βarrestin2 bias as a markedly beneficial feature for antiparkinsonian drugs, albeit underscoring the cooperative role of G proteins in mediating dopamine-induced motor behaviour. Thus, a full βarrestin2 ligand bias may not present an ideal pharmacological profile for the treatment of PD.

4.4. Signalling of pramipexole, ropinirole and rotigotine at the dopamine D_2 receptor

Given the importance of the D_2 receptor in treatment of PD, the biochemical responses elicited upon its stimulation with pramipexole, ropinirole and rotigotine were extensively studied, enabling the characterization of their efficacies, potencies, and functional selectivity. The detection of G protein activation in [^{35}S]GTPγS binding assays conducted in transfected Chinese hamster ovary (CHO) cells revealed that both pramipexole and ropinirole show efficacies comparable to dopamine (indicating full agonist properties) at the D_{2S} receptor, while their responses at the D_{2L} receptor were quantitatively lower when compared to dopamine, suggesting a partial agonist profile (Table 5) (Newman-Tancredi et al., 2002). For both receptor isoforms, the potencies of the two considered agonists were closely comparable to the potency of dopamine. However, the two dopamine agonists differed in their molecular efficacies, with ropinirole presenting a lower efficacy when compared to pramipexole (Table 5) (Newman-Tancredi et al., 2002). Extending the same experimental setup to rotigotine highlighted a remarkable potent and full agonism profile at all the D_2-class receptors, presenting a 200-fold higher potency at the D_{2L} receptor in comparison to dopamine (Table 5) (Scheller et al., 2009).

The [^{35}S]GTPγS binding approach provides useful insights on the ligand-induced activation of Gi and Go proteins in response to the activation of D_2-class receptors. Nevertheless, it does not allow to distinguish a potential difference in the activation of these two subtypes of G proteins. With the goal of overcoming this methodological limit, Laschet et al. adapted the nanoluciferase complementation technology to dynamically monitor the putatively distinct action of antiparkinsonian agents at the D_{2L} receptor when specifically focusing on the Gi1 and Go proteins recruitments (Laschet, Dupuis, & Hanson, 2019). The application of this assay in human embryonic kidney (HEK) 293 cells enabled to appreciate that both pramipexole and ropinirole shared full agonism for Gi1 recruitment and partial agonism for Go recruitment. Even though the readouts of both compounds were similar in regard to Gi1 proteins, pramipexole presented a 10-fold higher potency when compared to ropinirole in terms of Go recruitment at the D_{2L} receptor (Table 5). Exploiting the same experimental approach for the detection of the drug-induced interaction between the D_{2L} receptor and βarrestin2 revealed a full agonist profile for pramipexole and a partial agonist profile for ropinirole (Table 5) (Laschet et al., 2019). By calculating a bias factor for pramipexole and ropinirole in regard to Gi1, Go and βarrestin2, the authors could underscore a modest but significant βarrestin2 recruitment bias for pramipexole, while ropinirole displayed no appreciable difference between Gi1 or βarrestin2 recruitment at the D_{2L} receptor (Table 6). The moderate preferential recruitment of βarrestin2 over Go in response to pramipexole upon binding to the D_{2L} receptor was confirmed by bioluminescence resonance energy transfer (BRET), also performed in HEK 293 cells (Table 5) (Sanchez-Soto et al., 2020). Moreover, the same methodology indicated an even greater βarrestin2 recruitment bias in response to rotigotine (Table 6) (Sanchez-Soto et al., 2020), corroborating previous observations obtained comparing βarrestin2 and Gi/o signalling respectively through the PathHunter assay and the measure of cAMP accumulation performed in CHO cells expressing the D_{2L} receptor (Brust, Hayes, Roman, Burris, & Watts, 2015) (Tables 5 and 6).

At variance with the data reported by Laschet et al., another luciferase complementation assay measuring pramipexole-induced βarrestin2 recruitment in HEK 293 cells revealed a partial agonism profile at the D_{2L} receptor (Table 5) (Forster, Grätz, Mönnich, Bernhardt, & Pockes, 2020). Of note, measuring the physical interactions between βarrestin2 and the D_{2S} receptor by bioluminescence resonance energy transfer (BRET) in the same cell model depicted pramipexole as a full agonist, while ropinirole presented partial agonist features with a lower potency as compared to pramipexole (Table 5) (Klewe et al., 2008). Taken together, these studies highlight the profile of pramipexole and ropinirole as oscillating between full and partial agonist, according to the experimental approach used for their characterization in models of transfected cells. In terms of functional selectivity towards G protein or βarrestin2 recruitment, these studies

Table 5
Summary of the currently available literature describing the functional recruitment of Gi/o proteins or βarrestin2 at dopamine receptors in response to pramipexole, ropinirole and rotigotine. For each compound, the pharmacological parameters of efficacy (Emax) and potency (pEC_{50}) are hereby reported, together with the methodology of the study and the utilized cellular model.

Compound	Receptor	Assay	Experimental Model	Transducer	Efficacy (% of Dopamine)	Potency (pEC_{50})	Reference
Pramipexole	D_{2L}	Nanoluciferase complementation	HEK 293	Gi1	119	8.56	(Laschet et al., 2019)
	D_{2L}	Nanoluciferase complementation	HEK 293	Go	77	6.80	(Laschet et al., 2019)
	D_{2L}	Nanoluciferase complementation	HEK 293	βarrestin2	100	7.08	(Laschet et al., 2019)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (Low receptor density)	Gi1	135.94	9.88	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (High receptor density)	Gi1	119.01	10.03	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (Low receptor density)	βarrestin2	101.60	7.12	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (High receptor density)	βarrestin2	126.90	9.42	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Emerald luciferase complementation	HEK 293	βarrestin2	86	8.19	(Forster et al., 2020)
	D_{2L}	BRET	HEK 293	βarrestin2	103	7.19	(Sanchez-Soto et al., 2020)
	D_{2L}	BRET	HEK 293	Go	100	8.49	(Sanchez-Soto et al., 2020)
	D_{2L}	[^{35}S]GTPγS	CHO	Gi/o	70	6.47	(Newman-Tancredi et al., 2002)
	D_{2S}	[^{35}S]GTPγS	CHO	Gi/o	130	6.37	(Newman-Tancredi et al., 2002)
	D_{2S}	BRET	HEK 293	βarrestin2	104	7.55	(Klewe et al., 2008)
Ropinirole	D_{2L}	Nanoluciferase complementation	HEK 293	Gi1	106	8.23	(Laschet et al., 2019)
	D_{2L}	Nanoluciferase complementation	HEK 293	Go	73	5.89	(Laschet et al., 2019)
	D_{2L}	Nanoluciferase complementation	HEK 293	βarrestin2	79	6.54	(Laschet et al., 2019)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (Low receptor density)	Gi1	131.46	8.85	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (High receptor density)	Gi1	124.46	8.63	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (Low receptor density)	βarrestin2	N/A	N/A	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (High receptor density)	βarrestin2	N/A	N/A	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	[^{35}S]GTPγS binding	CHO	Gi/o	52	6.38	(Newman-Tancredi et al., 2002)
	D_{2S}	[^{35}S]GTPγS binding	CHO	Gi/o	108	6.18	(Newman-Tancredi et al., 2002)
	D_{2S}	BRET	HEK 293	βarrestin2	74	6.98	(Klewe et al., 2008)
Rotigotine	D_{2L}	[^{35}S]GTPγS binding	CHO	Gi/o	100	7.90	(Scheller et al., 2009)
	D_{2L}	BRET	HEK 293	βarrestin2	99	8.62	(Sanchez-Soto et al., 2020)
	D_{2L}	BRET	HEK 293	Go	100	10.00	(Sanchez-Soto et al., 2020)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (Low receptor density)	Gi1	161.75	9.82	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (High receptor density)	Gi1	147.80	9.74	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (Low receptor density)	βarrestin2	52.44	10.91	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	Nanoluciferase complementation	HeLa Tet-On D_{2L} (High receptor density)	βarrestin2	62.38	9.49	(Ferraiolo, Atik, et al., 2022)
	D_{2L}	PathHunter	CHO	βarrestin2	111	9.70	(Brust et al., 2015)
	D_{2L}	cAMP accumulation	CHO	Gi/o	95	10.70	(Brust et al., 2015)

assigned both pramipexole and ropinirole with a rather balanced profile at the D_{2L} receptor, with some tendency to preferentially promote βarrestin2 recruitment. Given the pivotal role of the βarrestin2/PP2A/PKB/GSK3β pathway in regulating locomotion, this signalling profile is in line with the clinical efficacy reported for both compounds at treating the motor symptoms of PD. In addition, the fact that ropinirole is currently considered as the most efficient dopamine agonist in terms of locomotor enhancement (Binde et al., 2020; Zhuo et al., 2017), these molecular insights of clinical efficacy in the treatment of PD. Indeed, G protein activation might also be required for the efficient preservation of motor performance, in accordance with what observed when observing the impact on motor behavior of G protein-biased and βarrestin2-biased mutant D_2 receptors expressed in murine models by viral reconstitution (Rose et al., 2018).

The signalling profile of ropinirole has been reported as presenting a potent full agonism when considering Gi1 and a less potent partial agonism when considering Go (Laschet et al., 2019), requiring a deeper exploration of the relationship between the functional selectivity of this compound and its clinical outcomes, notably on the modulation of locomotor behavior. It is noteworthy that ropinirole shares with pramipexole a full agonist profile at the D_{2S} receptor when assessing G protein recruitment while, for βarrestin2 recruitment, ropinirole showed reduced efficacy and potency (Klewe et al., 2008; Laschet et al., 2019; Newman-Tancredi et al., 2002). Although with discrete differences, the action of these ligands at presynaptic D_2 receptors might enable the regulation of the activity of the dopaminergic neurons in the substantia nigra and in the ventral tegmental area, providing the fine-tuning of the existent dopaminergic transmission with globally positive beneficial outcomes. Rotigotine differentiates itself from pramipexole and ropinirole by a marked preference for βarrestin2 recruitment at the D_{2L} receptor. Indeed, the robust activation of the PP2A/Akt/GSK3β pathway, in combination with a potent G protein full agonism, may underlie rotigotine's clinical efficacy at re-establishing motor performance in PD patients. Importantly, such βarrestin2 bias may compensate for the putative dyskinetic effects associated with the binding and activation of the D_1 receptor by rotigotine, providing an optimal balance between the locomotor effects conveyed by the activation of Gs/olf proteins and the risk of dyskinesias posed by the

Table 6
Summary of the experimental results estimating the functional selectivity of pramipexole, ropinirole and rotigotine in regard to Gi/o proteins or βarrestin2 recruitment at the D_2 receptor. The bias factor of each compound has been calculated using the operational model of agonism proposed by Kenakin et al (Kenakin et al., 2012). N/A; Not Applicable, as the authors could not measure any functional readout associated with the transducer of interest.

	Gi1		Go		βarrestin2		Bias Factor		
(Laschet et al., 2019)	Emax (% of dopamine)	pEC_{50}	Emax (% of dopamine)	pEC_{50}	Emax (% of dopamine)	pEC_{50}	Gi1 -Go	Gi1 - βarrestin2	Go- βarrestin2
Dopamine	100.00	8.64	100	6.6	100.00	6.75	0	0	0
Pramipexole	119.00	8.56	77.00	6.8	100.00	7.08	−0.09 (Go bias)	−0.33 (βarrestin2 bias)	−0.24 (βarrestin2 bias)
Ropinirole	106.00	8.23	73.00	5.9	79.00	6.54	0.46 (Gi1 bias)	−0.07 (βarrestin2 bias)	−0.53 (βarrestin2 bias)

	Go		βarrestin2		Bias Factor
(Sanchez-Soto et al., 2020)	Emax (% of dopamine)	pEC_{50}	Emax (% of dopamine)	pEC_{50}	Go- βarrestin2
Dopamine	100.00	8.49	100.00	7.33	0
Pramipexole	100.00	8.49	103.00	7.19	−0.13 (βarrestin2 bias)
Rotigotine	100.00	10.00	99.00	8.62	−0.23 (βarrestin2 bias)

	Gi/o		βarrestin2		Bias Factor
(Brust et al., 2015)	Emax (% of dopamine)	pEC_{50}	Emax (% of dopamine)	pEC_{50}	Go- βarrestin2
Dopamine	100.00	8.92	100.00	6.90	0
Rotigotine	95.00	10.70	111.00	9.7	−1.08 (βarrestin2 bias)

	Gi1		βarrestin2		Bias Factor
(Ferraiolo, Atik, et al., 2022) *Low receptor density*	Emax (% of dopamine)	pEC_{50}	Emax (% of dopamine)	pEC_{50}	Gi1- βarrestin2
Dopamine	100.00	8.05	100.00	7.60	0
Pramipexole	135.94	9.88	101.60	7.12	2.43 (Gi1 bias)
Ropinirole	131.46	8.85	N/A	N/A	Gi1 bias (Gi1 response only)
Rotigotine	161.75	9.82	52.44	10.91	−1.61 (βarrestin2 bias)

	Gi1		βarrestin2		Bias Factor
(Ferraiolo, Atik, et al., 2022) *High receptor density*	Emax (% of dopamine)	pEC_{50}	Emax (% of dopamine)	pEC_{50}	Gi1- βarrestin2
Dopamine	100.00	8.08	100.00	7.05	0.71 (Gi1 bias)
Pramipexole	119.01	10.03	126.90	9.42	0.43 (βarrestin2 bias)
Ropinirole	124.46	8.63	N/A	N/A	Gi1 bias (Gi1 response only)
Rotigotine	147.80	9.74	62.38	9.49	−0.43 (βarrestin2 bias)

downstream activation of its cognate pathway (Urs et al., 2015). This signalling footprint, together with the activation of D_4 and D_5 receptors, might indeed underpin a wide-ranging activation of dopamine signallings. As such, rotigotine would promote dopaminergic transmission homeostasis, laying the molecular foundation for the clinical efficacy and tolerability appreciated following the administration of rotigotine to PD patients (Binde et al., 2020; Zhuo et al., 2017).

Of note, by manipulating the receptor expression level in models of transfected cells, Ferraiolo et al. showed that the signalling bias of dopaminergic ligands, and especially dopamine agonists, is dependent on the density of the targeted receptor (Ferraiolo et al., 2022, b). In detail, when tested in a dedicated inducible system, pramipexole favoured Gi1 signalling at a low D_{2L} receptor density, while promoting the preferential recruitment of βarrestin2 at a high D_{2L} receptor density. On the other hand, the strong Gi1 bias of ropinirole appeared not influenced by the receptor expression level, while rotigotine showed a less marked βarrestin2 bias when tested at high receptor density (Table 6). The authors also showed that dopamine itself acquired a Gi1 bias at high receptor density, challenging the assumption postulating the balanced signalling of endogenous receptor ligands (Kenakin, Watson, Muniz-Medina, Christopoulos, & Novick, 2012.

These observations indirectly provide some possible explanation for the frequent discrepancies in the results obtained by different authors when characterizing the functional responses induced by receptor ligand. Indeed, beside the nature of the ligand, the associated signalling bias likely depends on several biochemical factors related to the experimental paradigm such as the receptor density, the host cell type where studies are conducted, the receptor/transducer stoichiometry, the membrane lipid composition or the presence of diverse intracellular proteins that influence the couplings (Hermans, 2003; Kenakin et al., 2012). Many of these receptor environment factors may evolve during the course of nervous disorders or after pharmacological treatments. Notably, the influence of D_{2L} receptor density on the pharmacological profile of dopamine agonists by might appear particularly relevant in the context of PD, as the striatal availability of D_{2L} receptors has been shown to significantly vary with the evolution of the disease and its pharmacological treatment. Brain imaging studies (Ichise et al., 1999; Kaasinen et al., 2000; Rinne et al., 1995; Verstappen, Bloem, Haaxma, Oyen, & Horstink, 2007) have highlighted that, when compared to control individuals, early-stage PD patients present higher striatal expression levels of D_{2L} receptors, likely resulting from their upregulation in response to the low dopaminergic tone. Conversely, late-stage PD patients show decreased levels of D_{2L} receptor, a phenomenon furtherly enhanced by chronic treatments with L-DOPA (Antonini, Schwarz, Oertel, Pogarell, & Leenders, 1997) or dopamine agonists (Politis, Wilson, Wu, Brooks, & Piccini, 2017). The clinical consequences of these changes in receptor density that likely drives the alteration in the functional selectivity of dopamine and dopamine agonists remain currently unknown. However, given their potential for therapeutic optimization, this topic deserves further investigation.

5. Concluding remarks

Pramipexole, ropinirole, and rotigotine present effective and safe options for the treatment of late PD, most commonly as adjunct to the administration of L-DOPA. These compounds have also been considered as valuable for delaying the initiation of L-DOPA-based therapies and their undesired consequences. Pramipexole and ropinirole appear as being slightly superior to rotigotine for the treatment of PD motor symptoms and PD-associated depression. However, rotigotine presents better tolerability features, with a reduced chance of causing motor complications, sleep attacks, or ICDs. The remarkable tolerability of

rotigotine can be attributed to its widely-encompassing pharmacological profile. Binding and activating all dopamine receptors as a potent full agonist, rotigotine might promote dopaminergic homeostasis, with holistically beneficial effects on brain transmission. On the other hand, the selectivity for D_2 and D_3 receptors shared by pramipexole and ropinirole may underpin their efficacy in the reestablishment of locomotor performance, albeit presenting the liability of an increased risk of undesired effect.

The analysis of the functional selectivity of these compounds at the D_2 receptor has revealed an overall picture, which, albeit fragmented, might indicate pramipexole and ropinirole as being slightly βarrestin2-biased agonists, with experimental or cell-related factors putatively shaping their signalling footprint. On the other hand, rotigotine seems characterized by a marked functional selectivity for βarrestin2 recruitment. These observations only partially reconcile the outcomes of clinical trials with the biochemically-oriented literature, which indicates βarrestin2-bias as the "silver bullet" for the treatment of PD. Indeed, according to this view, rotigotine, and not ropinirole, should be ranked as the most effective dopamine agonist for the treatment of PD. Such discrepancy might be explained by the considerable influence that experimental conditions exert when studying signalling bias, modulating the equilibrium between the intricated network of converging signalling pathways that can be activated by the same drug when acting at distinct GPCRs. In this context, it is important to highlight that all the aforementioned compounds bind D_3 receptors with high affinity, and that the characterization of the functional selectivity operating at this receptor are still to be unravelled. Hence, it is possible that shedding light on the molecular pharmacology of these compounds downstream of the D_3 receptor might reconcile preclinical and clinical observations obtained from studying dopamine agonists.

In conclusion, pramipexole, ropinirole, and rotigotine are effective means to counter the symptoms of PD. However, their prescription is not devoid of undesirable effects, calling for extensive research efforts, namely in the highly promising field of functional selectivity. Such studies might leverage the complexity of receptor signalling to envision the development of a novel class of antiparkinsonian agents capable of countering both motor and non-motor symptoms of PD with even more effective and tolerable profiles. Thereby, these new compounds would provide significant added value in a clinical setting, together with offering an improved quality of life to patients affected by the hardship of PD.

Declaration of Competing Interest

Emmanuel Hermans declares no conflict of interest. Mattia Ferraiolo is currently an employee of UCB Pharma S.A.® which had no influence on the original idea, manuscript writing, or the decision to submit the manuscript.

Acknowledgements

This work was supported by the Fonds de la Recherche Scientifique – FNRS.

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