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Plausible Improvements for Selective Targeting of Dopamine Receptors in Therapy of Parkinson's Disease

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Abstract: Parkinson's disease (PD) is a neurodegenerative condition characterized by progressive and profound loss of dopaminergic neurons in the substantia nigra pars compacta leading to the formation of eosinophillic, intracytoplamic, proteinacious inclusions termed as lewy bodies. L-dopa remains as a gold standard for the treatment of PD, and is often combined with carbidopa to reduce the dose-limiting side effects. Long-term levodopa treatment is associated with the development of motor fluctuations and peak dose dyskinesias. Dopamine Replacement Therapy (DRT) with dopamine agonists (DAs) (ropinirole and pramipexole) is used to manage complications of L-dopa treatment, however, has been associated with numerous pharmacovigilence reports. The present review attempts to narrate the multiple receptor interaction of DAs followed by the assessment of their side effects during the treatment of PD and possible remedial strategy for selective targeting of dopamine receptors to overcome these affects in therapy of Parkinson's disease.

Keywords: Apomorphine, Bromocriptine, Dopamine Replacement Therapy, Dopamine receptor, Ergolines, Non-ergolines.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative condition characterized by progressive loss of dopamine (DA) neurons in the substantia nigra pars compacta and affects 1% of the population worldwide over the age of 65 years [1]. Lewy body (LB) formation has been considered to be a marker for neuronal degeneration, and alpha-synuclein is a major constituent of LB fibrils. The formation of α-synuclein aggregates is a triggering event that causes tribulations in the proteasome, thus perturbing the protein disposal systems from its normal operating state [1]. Resting tremor, bradykinesia, postural instability, gait difficulty and rigidity are the main clinical manifestations of this complex disease. Based on the clinical symptoms, the disease may be classified as 1) Earlier onset - below age of 55 years at disease onset. 2) Tremor dominant- aged 55 years and over, tremor at rest as sole initial symptom or sustained dominance of tremor over bradykinesia and rigidity. 3) Non-tremor dominant – onset 55 years and over, predominantly bradykinetic motor features with no or only mild rest tremor. 4) Rapid disease progression without dementia- death within 10 years from first PD symptoms, irrespective of age; no dementia, but progression to advanced motor disability [2]. A multifactorial disease process in PD is caused by genetic, environmental, and other factors, and the symptoms begin to appear when 80% of the neurons get degenerated. The symptoms like anosmia, change of handwriting with micrographia, loss of arm swing on one side, sleep abnormalities, cardiac sympathetic denervation, constipation, depression, instability of syllable repetition and pain, may occur prior to the onset of signs of PD, and therefore may have diagnostic importance [3, 4]. The symptomatic relief with L-dopa still remains a standard treatment even almost 40 years after its introduction for the therapy of PD. L-dopa in combination with carbidopa reduces the dose-limiting side effects (eg, nausea and vomiting) related to the peripheral metabolism of the drug. Long-term L-dopa treatment leads to the development of motor fluctuations and dyskinesias. Treatment associated with side effects of L-dopa-induced dyskinesias (LID) emphasizes three primary clinical syndromes such as off-period dystonia, peak-dose dyskinesia and diphasic dyskinesia [5]. Therefore, L-dopa-sparing strategy involving dopamine agonists (DAs) monotherapy is used to delay L-dopa treatment [6]. The treatment of PD patients with DAs has although increased the quality of life, however, numerous pharmacovigilence reports documented the adverse consequences of dopamine replacement therapy (DRT) with dopamine agonists [7]. DRT results in changing the neural activity over the whole basal ganglia cortical networks, which disturbs the normal balance in the external globus pallidum (GPe)/internal globus pallidum (GPi) and fails to reinstate thereafter [8]. There are several books [9] and review reports [10] on the diverse type treatments for PD, the present review attempts to narrate the multiple receptor interaction of DAs followed by the assessment of their side effects during the treatment of PD and possible remedial strategy for selective targeting to DA receptors.

DOPAMINE (DA) RECEPTORS

Based on pharmacological and molecular properties, five distinct dopamine receptors have been identified [11, 12] and grouped into subfamilies as D1-like (D1 and D5) and D2-like

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(D2, D3, and D4) receptors. The comparative properties of five receptors have been illustrated from largely scattered data base [11] to critically assess the complications associated with the treatment of disorders related to DA receptors. DA, an endogenous neurotransmitter, acts on multiple receptor subtypes and DA neurons contribute to a wide range of complex sensory, motor, affective and cognitive functions in the normal organism through nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular DA pathways [11]. The primary sequence comparison of DA receptors revealed that D1 receptor are intronless and showed 82% homology to D5 receptor. Therefore, the development of selective ligands which discriminate between D1 and D5 receptors has posed a challenge. D1 and D5 receptors, are located mainly postsynaptically, whereas D2, D3 and D4 receptors, are found at both pre- and post-synaptic receptors. Furthermore, D1 receptor is 42-44% homologous to D2-like receptors and possesses short third intracellular loop and long carboxyl terminal tail. D2-like receptors possess long third intracellular loop and short carboxyl terminal tail, and exist in two isoforms namely short D_{2S} and long D_{2L}. The characteristic features of D1-like and D2-like receptors are elaborated in Table **1**.

SIDE EFFECTS ASSOCIATED WITH PD

DAs used for the treatment of PD exert their actions through DA receptors, and have been grouped into the ergolines (ERGs) and non-ergolines (NERGs). Both classes are, in general, equally effective in alleviating motor symptoms associated with PD, however, are coupled with severe complications due to their interaction with multiple receptors. Long term therapy with L-dopa causes dyskinesia [13], characterized by jerky, dance-like movement of the arms and/or head. Approximately, 50% of patients aged 45 years or less develop dyskinesia after L-dopa therapy [14]. However, role of dopamine D1 receptor agonism in PD is controversial due to contribution of D1 receptor related dyskinesia [49]. The first ergoline based DAs bromocriptine remained a popular choice for the treatment of PD till 2002. However, it has been reported to induce vulvular heart disease (VHD) and range of systemic fibrosis [15] including pleuritis, pneumonitis, pericarditis, raynaud syndrome, erythromelalgia and retroperitoneal fibrosis [16]. The mechanism of bromocriptine induced systemic fibrosis is unknown, however, bromocriptine may act at serotoninergic synapses to induce pleuropulmonary fibrosis [17]. Bromocriptine possesses structural similarity to methysergide (5-HT agonist), which is well known to cause pleuropulmonary fibrosis in carcinoid syndrome [18]. Most of the ergot compounds are partially specific and exhibit various 5-HT receptor affinities (*i.e.*, on the 5-HT2a receptor) with a consecutive stimulating impact on the regulation of the key mediator of fibrosis transforming growth factor-1, which can direct both proliferative and fibrotic signals in various mesothelial cell types [19]. The 8β-ergoline DAs, pergolide and cabergoline used for PD are alternative choice for the treatment of hyperprolactinemia at low doses. Although, pergolide was considered superior to bromocryptine in terms of duration of action and combined therapy with L-dopa, however, it caused pleuropulmonary and retroperitoneal fibrosis, and VHD [20], and was withdrawn by the US FDA [21]. Ergoline derived dopamine agonists exert their pharmacological actions, principally, by their partial agonistic interaction with D1, D2 and 5HT receptors [22]. The pathogenesis of dopamine agonist associated VHD in PD patients could be related to stimulation of 5HT2b receptor in human heart valve [22]. Moreover, the long term serotonin administration has been reported to cause the symptoms of VHD in rats [23], because 5HT2b receptors are plentiful in human cardiac valve, and ergot compounds are known to possess 5-HT receptor affinities (Table **1**). Valvulopathy-associated drugs induced serotonin production in cultured interstitial cells from human cardiac valves, which led to induce DNA synthesis via 5HT2b receptor activation [24]. Lisuride is used for treatment of PD, however has no link with fibrotic cardiac valvulopathy, and is in agreement with the 5HT2b receptor antagonist effect [25]. The pharmacovigilance reports related to side effects of ERGs and availability of NERGs derived DAs [26] made ERGs second line therapy for PD.

NERGs were developed in search of novel and receptor specific ligands due to multiple receptor interaction of ERGs in CNS leading to severe side effects. The clinical development of SCH-23390 was suppressed due to failure of D1 agonist SKF 38393 to reverse parkinsonism in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys to alleviate PD symptoms in humans [27]. Dihydrexidine [28], the first high affinity full efficacy agonist for the D1 and D5 receptors with approximately 10-fold selectivity over the D2 receptor revised the interest to develop D1-like agonists for the treatment of PD [29]. Subsequently a number of D1 agonists such as A-77636, dinapsoline, dinoxyline and doxanthrine were identified [30]. However, these compounds possessed insignificant anti-parkinsonian activity to cure the PD symptoms. Moreover, stimulation of D1-like receptors also caused the pathogenesis of postsynaptic neurodegeneration [54], which is linked to high extracellular levels of synaptic dopamine. DAs such as cabergoline, pergolide, pramipexole, and ropinirole, produce less dyskinesia compared with L-dopa over 3-5 years of therapy. These drugs reduce the dosing frequencies, have a longer half-life than L-dopa, reduce the dosing frequencies and well tolerated by most PD patients [31]. However, DRT either with L-dopa or NERGs is associated with behavioural side-effects such as impulse control disorders (ICDs) which significantly affect the sufferer's personal, family and occupational activity [32]. In recent years, numerous pharmacovigilance reports have appeared on ICDs associated with DRT in PD patients including pathological gambling [33], hypersexuality [34], compulsive shopping [35], internet addiction [36], compulsive smoking [37], compulsive hoarding [38], compulsive singing [39] and binge eating [40]. Risk factors for ICDs include male sex or younger age at PD onset, a pre-PD history of ICD symptoms, history of bipolar disorder and personality profile characterized by impulsiveness, pre-existing recreational drug or alcohol use and high novelty seeking personality traits [41]. In addition, ICDs have been viewed within the framework of obsessive-compulsive disorders (OCD) and as "behavioral addictions" with phenomenological and neurobiological similarities to chemical addictions [42]. Dropping head syndrome (DHS) in PD patients occurred

Table 1. Classification and Pharmacological Characteristics of Dopamine Receptors

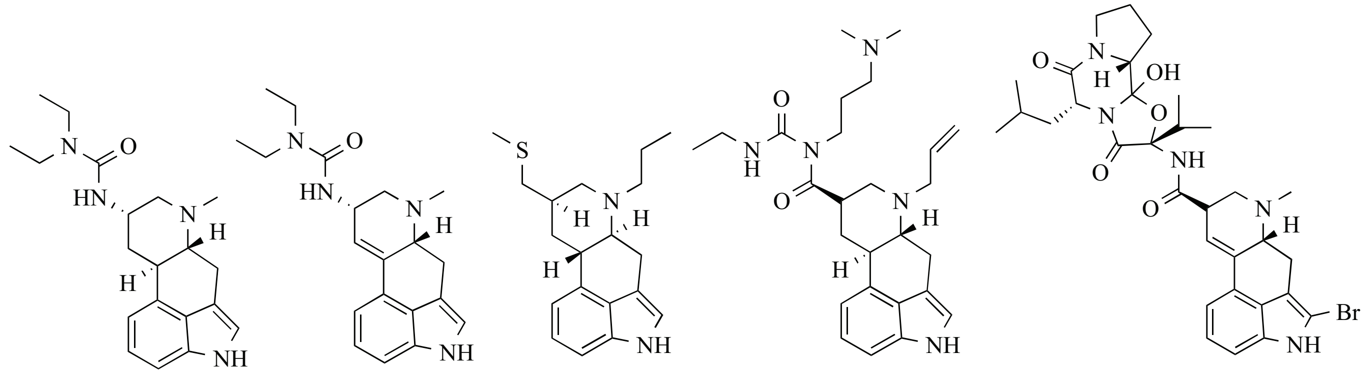
Features	***D1-Like***		***D2-Like***		
	D1	***D5***	***D2***	***D3***	***D4***
Gene	*DRD1*	*DRD5*	*DRD2*	*DRD3*	*DRD4*
GenBank number	P21728	P21918	P14416	P35462	P21917
Human Chromosome	5q35.1	4p15.2	11q23	3q13.3	11p15.4
Structural information	Intronless	Intronless	7 exons	7 exons	4 exons
Number of Amino acids	446 (h) 446 (r)	477(h) 475 (r)	D_{2L}: 443 (h) 444 (r) D_{2S}: 414 (h) 415 (r)	400 (h) 446 (r)	387-515 (h) 386 (r)
Signal transduction mechanism	cAMP (+)	cAMP (+)	cAMP (-)	cAMP (-)	cAMP (-)
Homology *1.D1 receptor*	100	82	44	44	42
2.D_{2S} receptor	44	49	100	76	54
Receptor distribution	caudate/putamen,nucleus accumbens, olfactory tubercle, hypothalamus, thalamus, frontal cortex	hippocampus, thalamus, lateral mamillary nucleus, striatum, cerebral cortex (all low)	caudate/putamen, nucleus accumbens, olfactory tubercle, cerebral cortex (low)	nucleus accumbens, olfactory tubercle, islands of Calleja, cerebral cortex (low)	frontal cortex, midbrain, amygdala, hippocampus, hypothalamus, medulla (all low), retina
Synaptic location	Postsynaptic		Both pre- and postsynaptic		
Agonists	SKF 38393	SKF 38393	Quinpirole, Bromocriptone	7-OH-DPAT, PD 128907	A-412 997
Antagonists	SCH 23390	SCH 23390	Spiperone, Haloperidol	SB-277011A	NGD-94-L A-381393
Pharmacological characteristics (Kd, nM)	SCH 23390 (0.35) dopamine (2340)	SCH 23390 (0.30) dopamine (228)	spiperone (0.05) raclopride (1.8) clozapine (56) dopamine (542)	spiperone (0.61) raclopride (3.5) clozapine (180) dopamine (24)	spiperone (0.05) raclopride (237) clozapine (9) dopamine (43)

h- human; r- rat; + stimulation; - inhibition, Source: IUPHAR database, [11].

after the initiation or loading of DAs (less common after pergolide than cabergoline and pramipexole) in some case [43]. Improvements noted after the reduction in the DAs dose in some patients, and loading of L-dopa in others [44]. Pedal edema among patients with PD is common with DAs of either class and history of coronary artery disease increases the risk for developing edema [45]. The cause of this edema could be related to secondary stimulation of peripheral dopamine receptors in the kidney or blood vessels [46]. It has been reported that L-dopa may act as endogenous neurotransmitter candidate of primary baroreceptor afferents and function to activate depressor neurons for regulation of blood pressure in rats [47]. Modulation in balance of pressure may result in edema [48]. Perhaps, peripherally acting dopamine receptor antagonist may reduce edema in PD patients.

INTERACTION OF ERGs WITH MULTIPLE MONOAMINERGIC RECEPTORS

The ERGs may be divided into 8α-aminoergolines as lisuride and terguride, and 8β aminoergolines as cabergoline and pergolide, with the exception of bromocriptine (Fig. **1**). Similarity in pharmacological properties (Table **2**) of ERGs may be related to their structural proximity in their pharmacophore. Pergolide and lisuride are agonists to all dopamine receptor subtypes, however, bromocryprine is antagonist to D1 receptor (Ki=1627 nM) whereas agonist to D2 receptor (Ki=2.5 nM). Interestingly, terguride is antagonist to D_{2L} receptor and agonists to D_{2S} receptor. Cabergoline has relatively high affinity for D1 type receptors in addition to D2-type receptor-agonist activity (Ki=200 nM).



Terguride **Lisuride** **Pergolide** **Cabergoline** **Bromocriptine**

Fig. (1). Structures of Ergoline DAs.

ERGs interact with all 5HT receptor subtypes. Agonistic interaction of ERGs to 5HT2b receptor accounts for the VHD, particularly with cabergoline (Ki=1.2 nM) and pergolide (Ki=7.1 nM). In contrast, lisuride acts as an antagonist (Ki =1.3 nM) to 5HT2b receptor, hence the chance of VHD is less with lisuride than other ergolines. Except pergolide, which acts an agonist, ERGs antagonistically interact with all α adrenergic receptor subtypes with high affinity and lisuride possesses relatively high affinity (Ki=0.055 nM) to α2a adrenergic receptor Table **2**.

The allied pharmacological profile of ERGs and their structural resemblance to natural endogenous biogenic amines could be related to manifold interactions with multiple receptors. The analogous molecular interface of ERGs with diverse receptor types are integrated into the ERG skeleton leading to subsequent side effects of DA agonists in confirmation of clinical observations (Fig. **2**).

NERGs DOPAMINE AGONIST AND RECEPTOR INTERACTIONS

Premier NERG such as apomorhine, administered subcutaneously, showed remarkable dopamine agonist activity [26], and laid the foundation for development of new NERGs (Fig. **3**), however, suffered with side effects such as nausea, akinesia etc. (Fig. **3**). Current treatment with pramipexole and ropinirole includes oral administion, while rotigotine is administered transdermally over a 24 hour period to provide continuous dopaminergic stimulation. All NERGs exhibit relatively high binding affinity to D3 receptors such as pramipexole (Ki=0.5 nM), ropinirole (Ki=2.9 nM), rotigotine (Ki=0.71 nM) and apomorphine (Ki=3.9 nM). Apomorphine and rotigotine are agonist to D1 receptor whereas others have negligible interactions at this receptor.

NERGs showed negligible interaction with other receptor subtypes except apomorphine which possessed partial resemblance with ERGs (Fig. **2**), Apomorphine acts as agonist to 5HT 1A receptor (Ki=117.5 nM) and antagonist to 5HT2A receptor (Ki=120.2 nM), moreover, it is agonist (Ki=141 nM) to α 2A and antagonist to α 2B (Ki=66.1 nM) and α 2C (Ki=36.3 nM) adrenergic receptors respectively (Table **3**). Generally, NERGs demonstrated high affinity and specificity to DA receptor subtypes and possessed low affinity for other monoaminergic receptors possibly due to inbuilt catechol ring system of dopamine (Fig. **3**). Ropinerole resembles the phenylethylamine structure of dopamine which is fused with electron rich pyrolidine-2-one, and with ethylamine side chain of dopamine. Similar structural resemblance of premipexole and rotigotine with dopamine has been demonstrated, however, rotigotine showed agonistic activity to 5HT 1A receptor (Ki=30 nM). The electron rich 2-aminothiazole ring in pramipexole and phenol ring in rotigotine resembles rigid ethylamine side chain of dopamine. The improved selectivity of NERGs towards dopamine receptors is exhibited by virtue of their simplified structure and lack of structural analogy to multiple neurotransmitters. Overall, NERGs structurally resemble each other by possessing structurally diverse bicyclic ring system with inbuilt phenylethylamine structure of dopamine.

NERGs also exhibited the classical side effects observed with L-dopa treatment such as dyskinesia. D1/D5 selective agonist SKF-81297 induced stronger dyskinesia than the D2 selective agonist quinpirole, moreover, dyskinesias may be decreased by treatment with a D1 antagonist clozapine [50], strongly supporting the possible participation of D1 like receptor in dyskinesia [49]. D1 receptor antagonists have exhibited strong antipsychotic potential in both rodents and nonhuman primates with a lesser potential for extrapyramidal side effects (EPS) in the form of dystonia and dyskinesia [51]. Stimulation of dopamine D3 receptors, primarily localized in the limbic system, participated mostly in reward seeking behavior [52], whereas psychosis and hallucination may be related to overstimulation of D2 and D4 receptors [53].

POSSIBLE THERAPEUTIC ADVANCEMENT FOR TREATMENT OF PD

In recent years, NERGs like pramipexole and ropindrole have emerged with negligible or no affinity towards D1-like receptors and possessed incredible antiparkinsonian activity, primarily through agonistic interaction with D2 and D3 receptors, thus demonstrating the important role of D2-like

Table 2. Receptor Binding Profile of Ergoline Dopaminergics (Ki in nMol/lit) [12]

Receptor Subtype	Bromocrptine	Cabergoline	Pergolide	Lisuride	Terguride
D1	1627 (An)	200 (Ag)	180 (Ag)	22 (Ag)	59
D2	2.5 (Ag)	0.69 (Ag)	0.2 (Ag)	0.29 (Ag)	0.19 (AnL,AgS)
D3	12.2 (Ag)	1.5 (Ag)	0.5 (Ag)	0.35 (Ag)	0.12 (Ag)
D4	59.7 (IA)	9.0 (Ag)	1.3 (Ag)	3.8 (Ag)	3.2 (An)
D5	1691	165	164	17.4	66.0
5HT1a	12.9 (Ag)	20.0 (Ag)	1.9 (Ag)	0.15 (Ag)	3.5 (Ag)
5HT1b	354.8 (Ag)	478.6 (Ag)	281.8 (Ag)	18.6 (Ag)	257 (Ag)
5HT1d	10.7 (Ag)	8.7 (Ag)	13.2 (Ag)	1.0 (Ag)	16.2 (Ag)
5HT2a	107.2 (Ag)	6.2 (Ag)	8.3 (Ag)	2.8 (Ag)	4.8 (Ag)
5HT2b	56.2 (PAg	1.2 (Ag)	7.1 (Ag)	1.3 (An)	7.1 (An)
5HT2c	741.3 (Ag)	692 (Ag)	295.1 (Ag)	6.6 (Ag)	47.9 (Ag)
α2A adrenergic receptor	11.0 (An)	12 (An)	50.1 (Ag)	0.055 (An)	0.30 (An)
α2B adrenergic receptor	34.7 (An)	7.2 (An)	32.4 (Ag)	0.13 (An)	0.45 (An)
α2C adrenergic receptor	28.2 (An)	22.4 (An)	67.6 (Ag)	0.13 (An)	0.76 (An)

Ag-agonist; An-antagonist; AnL-antagonist to long form; AgS- Agonist to short form; PAg-partial agonist; IA-inactive. Data reproduced from:[12].

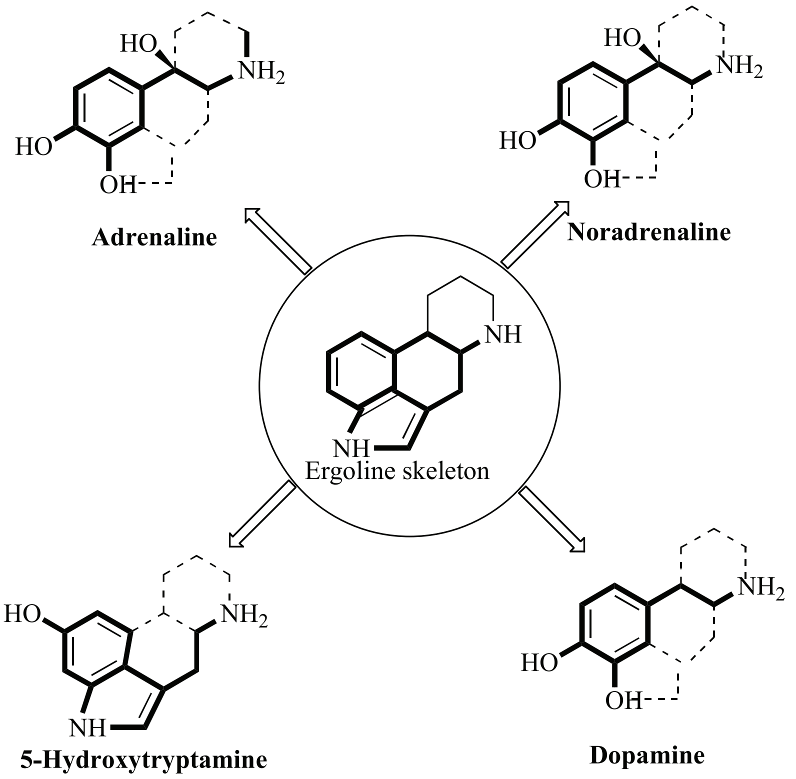


Fig. (2). Ergoline ring system and structural fragments of different neurotransmitters.

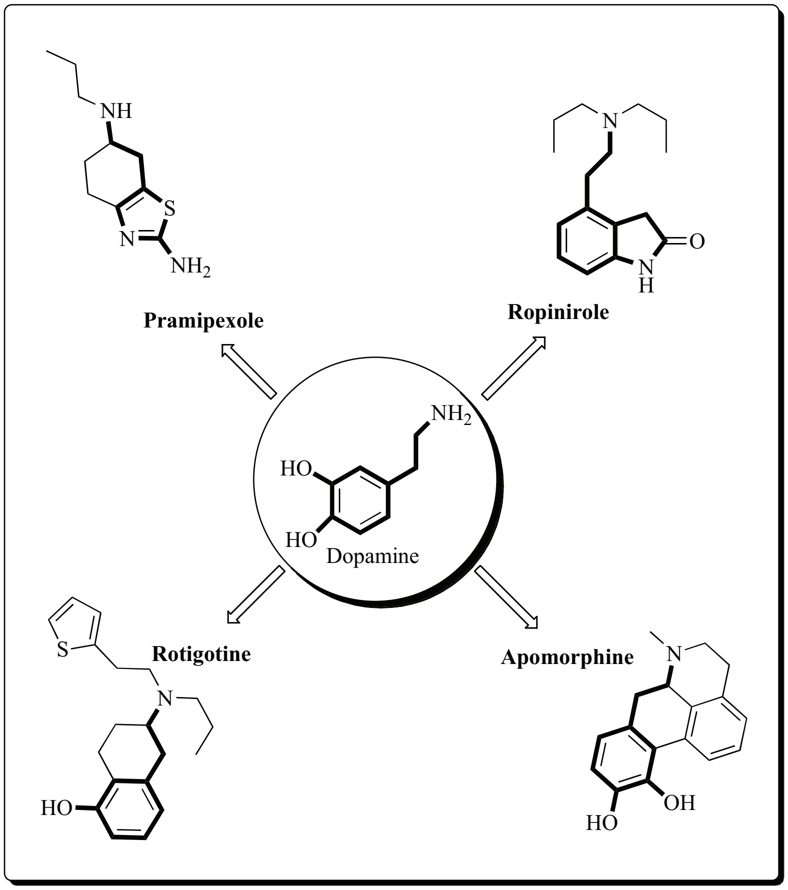


Fig. (3). Structural resemblance of NERGs to dopamine.

Table 3. Receptor Binding Profile of Nonergoline Dopaminergics (Ki in nMol/lit) [12]

Receptor Subtype	Pramipexole	Ropinirole	Rotigotine	Dopamine	Apomorphine
D1	>10 000	32 500	83 (Ag)	2340 (Ag)	154 (Ag)
D2	3.9 (Ag)	3.7 (Ag)	17 (Ag)	542 (Ag)	6.0 (Ag)
D3	0.5 (Ag)	2.9 (Ag)	0.71 (Ag)	24 (Ag)	3.9 (Ag)
D4	5.1 (Ag)	7.8 (Ag)	15 (Ag)	43 (Ag)	3.9 (Ag)
D5	>10,000	41,211	6.3 (Ag)	228 (Ag)	114
5HT1a	692	288	30 (Ag)		117.5 (Ag)
5HT1b	8318	>10,000			2951 (IA)
5HT1d	1660	1380			1203 (IA)
5HT2a	>10,000	>10,000			120.2 (An)
5HT2b	>10,000	3802			131.8
5HT2c	> 10,000	>10,000			102.3 (An)
α2A adrenergic receptor	1698 (PAg)	> 10,000(IA)			141 (Ag)
α2B adrenergic receptor	631 (IA)	> 10,000 (IA)			66.1 (An)
α2C adrenergic receptor	> 10,000 (IA)	> 10,000 (IA)			36.3 (An)

Ag-agonist; An-antagonist; PAg-partial agonist; IA-inactive. Data reproduced from:[12].

receptors for anti-parkinsonian activity. Stimulation of D2 receptors to exhibited restorative effects on denervated striatal D2 receptors in PD, however, undesired effects such as hallucination and psychosis related to D2 agonists may be mediated through stimulation of D2 receptors at other unaffected pathways [53]. Thus, the DAs stimulating the D2 receptor might be involved in anti-parkinsonian effects whereas dyskinesia might be depleted by the antagonism of the D1 receptor supporting a co-participatory role of the D1-like receptors in therapy of PD. Furthermore, D2 and D3 receptor agonists can delay the initiation of levodopa and can act synergistically with L-dopa to delay the onset of L-dopa-related motor complications and may have also neuroprotective effects [55]. Since, the affinity of dopamine varied in five receptor subtypes possessing lowest with D1 receptors (Ki= 2340 nM) and maximum for D3 receptors (Ki= 24 nM) (Table **1**), ideally, potential drug requires to possess dopamine like binding profile i.e. binding to all dopamine receptor subtypes with different binding affinity, for exerting distinct antiparkinsonian effects. Moreover, development of combination of DAs could be another approach in dilution of DRT related side effects, such as DAs possessing D1 antagonist and D2 agonist activity could be imperative approach in PD therapy. Furthermore, the neuroprotection by dopamine agonists pramipexole, ropinirole, pergolide, bromocriptine and apomorphine in cell cultures and animal models of injury to the substantia nigra demonstrated that dopamine agonists may have neuroprotective effects via direct scavenging of free radicals or increasing the activities of radical-scavenging enzymes, and enhancing neurotrophic activity. Furthermore, the finding that pramipexole can normalize mitochondrial membrane potential and inhibit activity of caspase-3 in cytoplasmic hybrid cells derived from mitochondrial DNA of patients with nonfamilial Alzheimer's disease suggests an even broader implication for the neuroprotective role of DAs [56]. Neuronal death involves cascade of molecular events due to increased levels of iron and monoamine oxidase (MAO)-B and nNOS activity, oxidative stress, inflammatory processes, glutamatergic excitotoxicity leading to abnormal protein folding and aggregation, reduced expression of trophic factors, depletion of endogenous antioxidants, and altered calcium homeostasis and may be responsible for the clinical heterogenicity in PD [2]. Moreover, the clinical outcome of the existing treatment may help to recognize clinical subtypes that might generate personalized or combined effects. Chronic treatment of human SK-N-MC neuroblastoma cells (endogenously expressing D1 dopamine receptors) with DA induces death of these cells. Treatment either with the antioxidant, sodium metabisulfite, or the D1 antagonist SCH 23390, was able to partially block the toxic effect of DA. When used together, these two agents completely blocked DA-induced cell death [57]. Importantly, activation of D1 receptors with the D1 agonist SKF38393 also killed neuroblastoma and striatal cells, and blockage of D1 receptor with selective antagonists displayed strong neuroprotective effects. The adjuvant and combination therapy with DAs is being explored as potential treatment relevant to specificity and severity of disease. Amantadine is a glutamate antagonist at NMDA receptors and has shown remarkable antidyskinetic effects mediated through the blockade of excitatory pathways in the basal ganglia [58], development of selective NMDA antagonists to block excitatory pathways together with sustained D2 receptor stimulation could be favorable in PD therapy. Adenosine receptor antagonists increase the therapeutic index ratio between the therapeutic and unwanted side effects of L-dopa and other D2R agonists. In addition, preclinical studies have raised the possibility that these therapies may afford neuroprotective and antidyskinetic benefits [58]. Ritanserin, a mixed 5HT2a/c receptor antagonist, has been shown to reduce bradykinesia and improvement of gait in PD patients, as well as ameliorate neuroleptic-induced parkinsonism. Nicotine sequestered the motor effects associated with L-dopa, and reduced L-dopa-induced dyskinesias. 5-iodo-A-85380 (A-85380) acts selectively at $\alpha4\beta2^*$ and $\alpha6\beta2^*$ subtypes, and reduce abnormal involuntry movements (AIMs) by 20%, while combination of A-85380 and varenicline, interacting with multiple nicotinic receptor (nAChRs), reduced L-dopa-induced AIMs by 40-50% in rats with a partial striatal dopamine lesion. Further, clinical exploration of 5HT2b receptor antagonists and therapeutic potential of nicotinic compounds for treatment of PD remains to be determined [59, 60]. It has been suggested that patients suffering from PD with a history of DAs induced fibrotic conditions should be re-exposed to pramipexole as a first choice to prevent premature onset of motor complications and faster progression of PD. All these disease modifying therapies are currently in clinical trials.

CONCLUSION

Regardless of the clinical heterogenicity of PD, the only effective treatment for management of PD to increase the patient's quality of life is DRT with DAs in combination with or without L-dopa. The multiple interaction sites for ERGs and structural diversity of NERGs to illustrate any SAR profile challenged the design of specific agonist for specific receptors. The ideal receptor binding profile is necessitated to reduce the side effects associated with DAs. The possible involvement of D1- like receptor in dyskinesia and postsynaptic neurodegeneration, suggests that D1 antagonists may be beneficial in the management of L-dopa induced dyskinesia. The agonistic stimulation of specific D2-like receptors and their neuroprotective effects in affected pathway may be optimal in PD. Development of ligand/s having less affinity with D1-like receptors and possessing selectivity and specificity to D2 like receptor along with NMDA and A2AR antagonists could be a positive approach in development of PD therapy. Recently, published crystal structure of D3 receptor [61] could be used to predict the structure of other subtypes to provide some insight into the binding of ligands to DA receptors [62] Therefore, structure based design in the development of better dopamine D2R agonist devoid of serious side effects could be rational approach for novel and advanced DAs.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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