ABSTRACT: Dopamine controls various physiological functions in the brain and periphery by acting on its receptors D1, D2, D3, D4, and D5. Dopamine receptors are G protein–coupled receptors involved in the regulation of motor activity and several neurological disorders such as schizophrenia, bipolar disorder, Parkinson’s disease (PD), Alzheimer’s disease, and attention-deficit/hyperactivity disorder. Reduction in dopamine content in the nigrostriatal pathway is associated with the development of PD, along with the degeneration of dopaminergic neurons in the substantia nigra region. Dopamine receptors directly regulate neurotransmission of other neurotransmitters, release of cyclic adenosine monophosphate, cell proliferation, and differentiation. Here, we provide an update on recent knowledge about the signalling mechanism, mode of action, and the evidence for the physiological and functional basis of dopamine receptors. We also highlight the pivotal role of these receptors in the modulation of neurogenesis, a possible therapeutic target that might help to slow down the process of neurodegeneration.

KEYWORDS: Parkinson disease, D1-like dopamine receptors, D2-like dopamine receptors, neurogenesis, behavioural functions

Introduction
Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease and approximately 1% to 2% population over the age of 60 to 65 years globally are affected by PD. The occurrence of PD generally ranges between 10 and 50/100,000 persons/year and the frequency increases sharply within the ageing population.1 A recent study using meta-analysis of worldwide clinical data indicates a growing incidence of PD with age (all per 100,000). Although this report also showed that PD prevalence at the age of 70 to 79 years significantly varies by geographical distribution, PD is less prevalent in Asia than in North America and European populations.2 However, there are very few population-based studies showing the prevalence of PD in Indian individuals. A survey performed in the Persian community in Mumbai showed a prevalence rate of 192 per 100,000 of PD, which was relatively higher compared with other regional populations of India.3 Clinical symptoms in PD involve motor and non-motor symptoms. The motor impairment in parkinsonism includes a number of altered movements, including bradykinesia, resting tremors, rigidity, and postural instability,1 whereas non-motor symptoms include constipation, fatigue, sexual dysfunction, olfactory deficits, sleep disturbances, anxiety, depression, and an impairment in learning and memory.5

The nigrostriatal pathway is a main dopaminergic (DAergic) pathway that connects the substantia nigra (SN) to the caudate and putamen nucleus of the dorsal striatum. Brains affected by PD present with degeneration of DAergic neurons in the SN (SNpc) region as well as a loss of dopamine neurotransmitter in the dorsal striatum. The available treatments for PD only provide symptomatic relief and do not slow or halt the neuro-degenerative process, thus they are not curative or preventive. Levodopa (l-DOPA) is gold standard therapy for PD, but its chronic use results in the development of motor complications, often termed as l-DOPA–induced dyskinesias.6,7 Dopamine functions by acting on DAergic receptors, which are classified as D1-like receptors (D1 and D5) and D2-like receptors (D2, D2, and D4).8,9 Currently, DA receptor agonists are the first choice of treatment for patients with PD, which delays the onset of l-DOPA therapy. The DA receptor agonists are also used in a combination with l-DOPA to treat motor complications in advanced stages of PD.10

Dopaminergic neurons originating from the SN (SNpc) and ventral tegmental area (VTA) directly innervate the hippocampus and subventricular zone (SVZ), a niche for neural stem cells (NSCs), suggesting a functional and anatomical connection of dopamine with distal brain regions. There are 2 well-identified neurogenic regions in the mammalian brain: subgranular zone (SGZ) in the hippocampal dentate gyrus (DG) and SVZ, where newborn neuron formation takes place.11 The formation of newborn neurons from NSCs is termed as ‘neurogenesis’, which is a finely tuned conserved process throughout the mammalian lifespan. Dopamine receptors are widely expressed in the hippocampal DG and SVZ region and are actively involved in the modulation of neurogenesis in basal forebrain structures, thereby supporting the hypothesis that dopamine plays a role in neurogenesis and brain plasticity.12 For example, dopamine denervation in the SN significantly reduces NSC proliferation in the SVZ and SGZ in...
mice, whereas pharmacologic D2 receptor stimulation significantly recovers NSC proliferation.13 Recently, using a pharmacologic approach, it has been shown that ropinirole, a partial D2 agonist, did not affect hippocampal NSC proliferation, whereas the D3 agonist pramipexole significantly increased NSC proliferation and neuronal differentiation in adult rat hippocampal DG.14 Studies have shown that 6-hydroxydopamine (6-OHDA) induced dopamine depletion in the SN (SNpc) leads to decreased NSC proliferation in SVZ and SGZ in rodents.15-17 In contrast, D2/D3 receptor stimulation did not show any effect on NSC proliferation and DAergic neuronal differentiation in murine and human brain–derived neural progenitor cells (NPCs).18 Interestingly, a study showed that MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)–induced dopamine depletion in the midbrain transiently increased NSC proliferation and postmitotic neuronal differentiation in hippocampal DG in mice.19 In contrast, a recent study demonstrated no change in NSC proliferation and newborn neuron formation in the hippocampus following the treatment of 6-OHDA in adult rats.20 Neurogenic potential of NSCs in the brain is compromised during neurodegeneration as decreased proliferation of NSCs in DG and SVZ has also been reported in patients with PD,13 suggesting that dopamine signalling regulates adult neurogenesis, but this notion requires further research to demonstrate the precise mechanism of action of dopamine.

Physiology of Dopamine Receptors

Dopamine is a monoamine catecholamine neurotransmitter belonging to the 7 transmembrane G protein–coupled receptors (GPCRs), which play an important role in the regulation of not only motor functions but also non-motor functions such as motivation, cognition, emotion, and neuroendocrine secretion.21 Dopamine acts on dopamine receptors to regulate motor and non-motor function in a specific manner. The existence of dopamine receptors was revealed in 1972 and it was indicated that dopamine stimulates adenylyl cyclase (AC) activity.22,23 Pharmacologic and biochemical studies showed that dopamine has multiple binding sites,24 suggesting that 2 population of dopamine receptors are present: one is positively coupled to AC and other is independent of AC.25 Thereafter, Kebabian et al25 subsequently classified dopamine receptors into 2 families, D1-like receptor and D2-like receptor, on the basis of pharmacologic properties and the ability to regulate cAMP (cyclic adenosine monophosphate) generation. In the human central nervous system (CNS), the relative density of DA receptors is D1 > D2 > D3 > D5 > D4.26 The regional expression in the brain, mechanism of action, behavioural functions, and the selective agonists and antagonists of different types of dopamine receptors are described in Table 1. Dysfunction of dopamine neurotransmission and its receptors leads to several pathological conditions, such as hyperprolactinaemia, PD, schizophrenia, Tourette syndrome, attention deficit/hyperactivity disorder, and Huntington disease.27-30 Dopamine receptor agonists and antagonists are used to alleviate symptoms associated with these conditions.

D1-like dopamine receptor expression and its functions

The D1-like receptor family consists of 2 types of GPCRs that include the D1 and D5 receptors, with a higher density in the striatum or caudo-putamen, nucleus accumbens (NAcc), SN pars reticulata (SNr), and olfactory bulb (OB).31,32 A moderate expression of D1 receptors has been reported in the entopeduncular nucleus, cerebral aqueduct, and ventricles,33 with a lower density in the dorsolateral prefrontal cortex, cingulate cortex, and hippocampus.34 D1 receptors play an important role in the regulation of the reward system, locomotor activity, learning, and memory.35 Typically, D1 receptors induce the stimulation of AC activity through the activation of guanosine nucleotide–binding proteins (G proteins) and produce cyclic AMP as a secondary messenger (Figure 1). D1 receptors are also involved in signal transduction pathways that are linked to various neuropsychiatric disorders, activating the phospholipase C and inducing intracellular calcium release.36 Calcium is not only involved in the regulation of the signalling pathway that causes the activation of proteins, such as calcium–dependent protein kinase C (PKC), but it is also involved in the modulation of neurotransmitter release by exocytosis.36 D1 receptors regulate the electrochemical gradient through Na⁺/K⁺-ATPase. It has been shown that the activation of D1Rs inhibits Na⁺/K⁺-ATPase through protein kinase A (PKA) and PKC signalling pathways in the striatum37,38 and in the kidney.39

D2-like Dopamine Receptor Expression and Its Functions

The D2-like dopamine receptor family is classified into D2, D3, and D4 subfamilies. D2R subtypes have 2 isoforms: the D2-short and D2-long type receptors. The D2 receptor and its subtypes are expressed in the brain, mainly in striatum, external globus pallidus (GPe), core of NAcc, amygdala, cerebral cortex, hippocampus, and pituitary.40 Expression of messenger RNA D2R is present in prefrontal, temporal, and entorhinal cortex, in the septal region along with the VTA and SN (SNpc) of DAergic neurons.39 The activation of this family of receptor typically inhibits the activation of AC activity and also inhibits the production of cAMP levels and PKA (Figure 2).41-43 D2 receptors play an important role in postsynaptic receptor–mediated behavioural and extrapyramidal activity. D2 receptors are autoreceptors that are either somatodendritic autoreceptors, which are known to decrease neuronal excitability,44,45 or terminal autoreceptors, which mostly reduce DA synthesis and packaging46,47 and inhibit dopamine release. It has been suggested that during the embryonic stage, the D2 autoreceptor may play a role in DA neuronal development.48 D2 receptors activate cell proliferation–related pathways, such as the
mitogen-activated protein kinase (MAPK) and Akt (thymoma viral proto-oncogene also known as protein kinase B) signalling pathways.\textsuperscript{49,50} Activation of D3Rs enhances Akt activity, which increases the dendritic arborization in DAergic neurons from the mouse embryos.\textsuperscript{51}
Differentiation into neurons and glia. Expression of cell surface markers on neuronal and nonneuronal cells.

**Table 2.** Different types of cellular markers expressed on neuronal and nonneuronal cells.

| PROCESS                  | MARKERS                                      |
|--------------------------|----------------------------------------------|
| Cell proliferation       | PCNA, Ki-67                                  |
| Neuronal migration       | DCX, PSA-NCAM, Reelin                       |
| Maturation               | Neurons – NeuN, Tuj-1, Calbindin Astrocytes – GFAP, S100B, GLT-1 Oligodendrocytes – MBP, Sox-10, OSP |

| CELL TYPES               | MARKERS                                      |
|--------------------------|----------------------------------------------|
| Immature neurons (neuroblasts) | DCX, NeuroD1, TBR-1                           |
| Neural stem cells (NSCs)  | Sox-2, Nestin, Pax-6, Mash-1                  |
| Oligodendrocyte precursor cells (OPCs) | Olig-1, Olig-2, NG-2, PDGFR-α                 |
| Radial glia-like stem cells (RGCs) | Sox-2, GFAP, Nestin, Vimentin, nestin, Pax6, HESt, BLBP |
| Microglia                | CD45, Iba-1, F4/80                            |
| Dopamine neurons         | TH, Nurr-1, Phtx-3                            |

**Neurogenesis**

In the early 1960s, it was thought that neurons do not regenerate in adults. For the first time, Altman and Das proposed the existence of newly generated neurons in the hippocampus of postnatal rats in the 1960s, but this study was ignored by the scientific community. Later, this study was further supported by the evidence of generation of new neurons in the DG region of the rat brain. Furthermore, the study by Goldman and Nottebohm broke the misconception that neurogenesis is limited to an embryonic phase by showing evidence of adult neurogenesis in song birds. In a few years, researchers have focused on underlying mechanisms and factors behind postnatal neurogenesis. Later, in the 1990s, new methods have been discovered for the labelling and identification of proliferating and dividing cells, such as retroviruses and bromodeoxyuridine (BrdU), a thymidine analogue that incorporates into DNA during the synthetic phase (S-phase) of the cell cycle. BrdU was introduced to study neurogenesis in the adult CNS. Using these methods, for the first time, Eriksson et al showed evidence of the formation of newborn neurons in the adult human hippocampus and also demonstrated that the new neurons were generated from dividing neural progenitors in the DG. The cell proliferation, neuronal migration, neuronal differentiation, and different cellular markers are classified in Table 2. There are 2 well-studied and known regions in the brain, SVZ of lateral ventricles (LVs) and SGZ of hippocampal DG, where proliferating cells migrate to a given destination to further differentiate into neurons and glia. Expression of cell surface adhesion molecules is very important for the migration of neuronal cells in the SVZ-rostral migratory stream system. However, balanced neurogenesis in both major neurogenic regions of the adult mammalian species depends on the maintenance of the NSC pool, which is firmly controlled by their specialized local microenvironment.

**Major Factors Regulating Neurogenesis**

The fundamental capacity of stem cells to self-renew and their multipotency maintains NSC pool during postnatal stages. Although some external and endogenous stimuli restore neurogenesis by increasing the number of NPCs, it is generally found to decline with age, indicating that NSCs also modulate the neurogenic niche. Neurotransmitters such as dopamine, serotonin, and glutamate are important for the regulation of adult and embryonic neurogenesis.

**Dopamine and Its Receptors in Adult Neurogenesis**

On top of its role in motor control, mood and as a neurotransmitter, dopamine also plays a crucial role in neuronal proliferation and differentiation in the adult CNS. The DAergic projections directly innervate the SVZ and hippocampus, thus directly influencing the microenvironment of these niches to regulate NSC dynamics. Kippin et al have suggested that chronic treatment with the D2-like antagonist, haloperidol, in adult rats led to an increase in the number of primary neurospheres obtained from the SVZ. However, treatment with dopamine or the D2-like agonist, quinpirole led to the formation of fewer subsequent neurospheres. Hence, these results suggest that dopamine inhibits the proliferation of NSCs (B cells). However, no evidence was reported for an alteration of B-cell proliferation by dopamine depletion in vivo. Studies have demonstrated that systemic treatment of D2-like agonists ropinirole or 7-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OH-DPAT) in normal and dopamine-depleted rats significantly increased precursor cell proliferation in the SVZ. Similarly, l-DOPA also significantly increased SVZ cell proliferation in the dopamine-depleted rats. Alteration in midbrain dopamine neurons by 6-OHDA or MPTP toxin decreased proliferation and differentiation of NSCs in the SVZ and hippocampus of rodents. The role of dopamine signalling is further confirmed by dopamine receptor-mediated regulation of neurogenesis; for example, D1 receptor agonist treatment significantly increased hippocampal neurogenesis, whereas D2 receptor agonist treatment did not have an effect on progenitor cell proliferation and survival of hippocampal neurons in adult rats. Similarly, MPTP disrupted the D1 receptor-mediated adult hippocampal neurogenesis and survival of neurons as well as induced depression-like behaviour in mice, suggesting an important functional control of dopamine receptors on NSC dynamics and birth of newborn neurons. Interestingly, several studies using a pharmacologic approach have shown contradictory results. For example, D2 receptor stimulation potentially increased NPC proliferation in the SGZ and SVZ in mice and in vitro. In contrast, treatment with haloperidol, a D2 antagonist significantly increased NSC proliferation and the number of...
neurons and glia in the adult rat brain, whereas D2 receptor stimulation in vitro attenuated the effect of the D2 antagonist, haloperidol, suggesting a negative role of dopamine signalling in adult neurogenesis. Interestingly, Takamura et al showed no effect on NSC proliferation and neuronal survival in the adult rat hippocampus. In the 6-OHDA–induced rat model of PD, the D2/D3 receptor agonist pramipexole increased DAergic neurogenesis in the SVZ–OB system by regulating the transcription of epidermal growth factor and paired box gene 6 (Pax-6). In contrast, pharmacologic inhibition or genetic ablation of the D3 receptor failed to affect adult neurogenesis in mice.

**Improvement of the DAergic System by Adult Neurogenesis**

In PD, pharmacologic replacement therapy has provided temporary symptomatic relief. Both neuroprotective and cell replacement therapy are also being explored. The hypothesis that neurogenesis in the adult brain could repair the nigrostriatal DAergic system has received significant attention in recent years, but this hypothesis still remains highly controversial.

In 2002, the evidence for proliferating progenitor cells in the SN was demonstrated in adult rats. It was observed that the dividing progenitors gave rise to mature glial cells but not to newborn neurons in the SN. Under physiological conditions, newly generated neurons in the SN originate from the ventricular system and approximately 20 new neurons are added per day in the SN in rodents. Some previous studies have reported that polysialated-neural cell adhesion molecule (PSA-NCAM), a marker of immature neuroblasts, is detected in post-mortem SN of human patients with PD. However, PSA-NCAM is also expressed in glial cells and neurites of neurons and it maintains neuronal plasticity. Hence, these findings show that some degree of cellular plasticity is maintained in the SN region even in the aged human patients with PD. Shan and co-workers have reported de novo neurogenesis and DA neurogenesis in the SN of adult control and MPTP-treated mice. Studies suggest that increased NPCs in the MPTP-lesioned mice promote de novo neurogenesis, which may prove to be an effective therapy for PD by providing functional replacement of degenerated DAergic neurons. Other studies have reported that neurogenesis in the SN of adult rats creates progenitor cells and these progenitor cells differentiate into glial cells, oligodendrocytes, and neuronal cells. Interestingly, it has been also shown that isolated NSCs from the mouse adult tegmentum have the capacity to generate DAergic neurons in vitro. Cultured adult human neural progenitors from the SN of patients with idiopathic PD have the ability to differentiate into glia and neurons (even in TH-DAergic neurons), suggesting that the SN possesses neurogenic potential which is highly dependent on local, microenvironmental clues. In line with this evidence, we have reported reduced NSC proliferation, self-renewal capacity, and neuronal differentiation in the SVZ and hippocampal DG that involve the downregulation of Wnt/β-catenin signalling in the 6-OHDA–induced rat model of PD-like phenotypes. Interestingly, 6-OHDA–induced injury in the SN of adult control and MPTP-treated mice; hence, it is reasonable to propose that chronic D3 receptor stimulation with 7-OH-DPAT triggers a strong induction of cell proliferation in the rat SN and promotes the expression of DAergic neurons.

In contrast, several groups have unsuccessfully tried to obtain evidence of spontaneous generation of BrdU+ TH+ neurons in the SN of control, unlesioned adult rats and mice and even after the infusion of growth factor in experimental models of PD, thus suggesting that the effect of DA signalling on neurogenesis is also regulated by other endogenous molecules other than DA receptors and the precise mechanism underlying the effect of DA receptors is still not known.

**Other Factors Control Formation of Newborn Neurons**

The level of neurotransmitters, including dopamine, serotonin, γ-aminobutyric acid, and glutamate, collectively regulate behavioural responses, perception, cellular fate, and neurogenesis. Moreover, the levels of serotonin, GABA, and glutamate are significantly altered in the brain during PD pathogenesis, which leads to several manifestations such as dyskinesia, cognitive impairment, and mood alterations, suggesting that the fine-tuned balance among all neurotransmitters is essentially required for neuronal communication. Serotonin or 5-hydroxytryptamine is a biological monoamine neurotransmitter that is thought to be responsible for happiness and well-being. Reduction in serotonin by lesioning serotoninergic neurons leads to depletion of adult neurogenesis in the DG and SVZ region, suggesting a stimulating role for serotoninergic neurons in neurogenesis. Interestingly, the administration of fluoxetine, a selective serotonin reuptake inhibitor, enhanced...
hippocampal NSC proliferation and neurogenesis in the rat model of PD. In postnatal SVZ and SGZ, expression of glutamate receptors is found on neuroblasts rather than stem cells during migration to the OB and these migrating neuroblasts are protected by specialized astrocytic cells that release glutamate. Preceding studies using knockout of NMDA (N-methyl-D-aspartate), a glutamate receptor agonist, receptors found that NMDA knockout resulted in apoptosis of migrating neuroblasts. In contrast, NMDA, treatment significantly increased the proliferation of human mesencephalic-NPC and their differentiation into tyrosine hydroxylase-immunopositive cells, whereas the effect of NMDA was attenuated by the treatment with memantine, an NMDA receptor antagonist, suggesting that NMDA receptors are crucial regulators of DAergic neurogenesis in vitro.

**Therapeutic Strategies of Dopamine and Its Receptor in PD**

Levodopa is a gold therapy for the treatment of PD, but chronic treatment with L-DOPA induces motor fluctuation (such as wearing-off and on phenomena) and involuntary movements (such as dyskinesia and dystonia) that could appear in patients with PD. Currently, DA receptor agonists are the first choice to delay onset of the adverse effects of L-DOPA in young onset patients with PD. The pharmacologic effects of DA receptor agonist is directly activating DA receptors, thus bypassing the presynaptic synthesis of DA. The half-life of DA receptor agonist and antagonist are longer than L-DOPA; therefore, they can produce a more persistent period of DA receptor stimulation than L-DOPA. Dopamine receptor agonists are neuroprotective agents, acting as a free radical scavenger, reducing DA synthesis, DA release, and also exerting antiapoptotic effects via the activation of presynaptic autoreceptors. Clinical studies have suggested that activation via D1 receptor agonist is beneficial in the treatment of PD. Bromocriptine, a D2 receptor agonist, is shown to protect mice against 6-OHDA and to scavenge methamphetamine-induced free radicals and also exerts neuroprotective effects against glutamate-induced cytotoxicity in rat mesencephalic and cortical neurons. Similarly, cabergoline, a dopamine agonist, in a combined therapy with low doses of L-DOPA showed beneficial effects in treating patients with PD. The combination of cabergoline and L-DOPA is highly effective in controlling motor disability without inducing dyskinesia in MPTP-lesioned parkinsonian cynomolgus monkeys. Nomoto et al. reported protective effects of lisuride in the dermal application on MPTP-treated marmosets and on 5 patients with PD. This agent relieved akinesia and parkinsonism in MPTP-treated monkeys and increased the duration of the ‘on’ period in patients with PD. Ropinirole, a nonergoline agonist and having a high affinity for D2 and D3 DA receptors, was reported to be very effective in early and advanced PD. However, in animal models of PD, ropinirole demonstrated reverse effects on motor and behavioural deficits.

**Conclusions**

The studies described here indicate the significant efforts made by the scientific community in understanding the biology, mode of action, targets, functions, and signalling mechanisms of dopamine and its receptors. Due to a lack of suitable targets and inadequate knowledge, the overall clinical implications or translation of available information is very limited. To compensate the degenerative rate of DAergic neurons, we have only 2 choices, either enhance the formation of newborn neurons and endogenous regenerative capacity or reduce the death rate of existing neurons. Dopamine receptors are expressed on proliferating cells and newborn neurons and thus directly govern the multiple steps of neurogenesis. Therefore, understanding the precise role of dopamine receptors in the development of newborn neurons and in non-motor symptoms could be a therapeutic strategy for the treatment of dopamine-related neurological disorders.

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**Author Contributions**

AM, SS wrote the review and ShS conceptualized and edited the review.

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