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Review

Dopamine D1–D5 Receptors in Brain Nuclei: Implications for Health and Disease

Ichiro Kawahata [1,*], David I. Finkelstein [2] and Kohji Fukunaga [1]

[1] Department of CNS Drug Innovation, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8578, Japan; kfukunaga@tohoku.ac.jp
[2] Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, VIC 3010, Australia; david.finkelstein@florey.edu.au
* Correspondence: kawahata@tohoku.ac.jp; Tel.: +81-22-795-6838; Fax: +81-22-795-6835

Abstract: Understanding the intricate role of dopamine D1–D5 receptors is pivotal in addressing the challenges posed by the aging global population, as well as by social stress and advancing therapeutic interventions. Central to diverse brain functions such as movement, cognition, motivation, and reward, dopamine receptors are ubiquitously distributed across various brain nuclei. This comprehensive review explores the nuanced functions of each dopamine receptor, D1, D2, D3, D4, and D5, in distinct brain regions, elucidating the alterations witnessed in several neurological and psychiatric disorders. From the substantia nigra and ventral tegmental area, crucial for motor control and reward processing, to the limbic system influencing emotional responses, motivation, and cognitive functions, each brain nucleus reveals a specific involvement of dopamine receptors. In addition, genetic variations in dopamine receptors affect the risk of developing schizophrenia and parkinsonism. The review further investigates the physiological significance and pathogenic impacts of dopamine receptors in critical areas like the prefrontal cortex, hypothalamus, and striatum. By unraveling the complexities of dopamine receptor biology, especially those focused on different brain nuclei, this review provides a foundation for understanding their varied roles in health and disease, which is essential for the development of targeted therapeutic strategies aimed at mitigating the impact of aging and mental health on neurological well-being.

Keywords: dopamine D1 receptor; D2 receptor; D3 receptor; D4 receptor; D5 receptor; striatum; cortex; subthalamic nucleus; amygdala; hippocampus; substantia nigra; ventral tegmental area

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1. Introduction

The aging global population presents a profound challenge to healthcare systems worldwide, necessitating a deeper understanding of the molecular intricacies governing neurodegenerative processes. Among the key players in the intricate network of neuronal signaling are dopamine receptors, integral components orchestrating a symphony of physiological responses. Dopamine, a neurotransmitter renowned for its central role in motor control, reward mechanisms, and cognitive functions, engages a diverse family of receptors, each with distinctive functions and implications for human health. Dysregulation and genetic variations in dopamine receptors affect the risk of dopaminergic pathogenesis, including mental and movement disorders.

Since there have been few reviews that have presented the function of dopamine receptors based on different brain nuclei, this review focuses on the distribution of dopamine D1–D5 receptors, based on each brain nucleus, their physiological significance, and their relevance to disease. Therefore, this review aims to comprehensively explore the multifaceted roles of dopamine D1, D2, D3, D4, and D5 receptors, delving into their intricate functions within the central nervous system, particularly in the different nuclei of the brain, and the implications in disease. Beyond their well-established contributions to motor coordination, emerging evidence implicates these receptors in a spectrum of neurodegenerative diseases, including

motor and cognitive dysfunctions, as well as psychiatric disorders, including Parkinson's disease, dystonia, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD).

As we stand at the intersection of an aging population and unprecedented strides in therapeutic development, elucidating the nuanced involvement of dopamine receptors in health and disease becomes paramount. Thus, through an in-depth examination of the current literature, we seek to provide a comprehensive overview of the physiological impacts of nuclei-dependent dopamine D1–D5 receptors, shedding light on their potential as therapeutic targets, and unraveling the complexities that underscore their pivotal role in neurological well-being.

2. Types, Characteristics, and Regulation of Dopamine Receptors

Dopamine receptors, integral components of the central nervous system, form a diverse class of G protein-coupled receptors that mediate the actions of dopamine. Categorized into D1-like (including D1 and D5) [1–5] and D2-like (encompassing D2, D3, and D4) receptor families [6–10], these receptors exhibit distinct structural and functional characteristics. D1-like receptors, such as D1 and D5, predominantly elicit excitatory effects by activating adenylate cyclase and increasing intracellular cyclic AMP (cAMP) levels [11]. Conversely, D2-like receptors, including D2, D3, and D4, typically exert inhibitory effects by inhibiting adenylate cyclase and decreasing cAMP levels [12]. The distribution of these receptors is heterogeneous throughout the brain, with specific subtypes being concentrated in different regions, thus contributing to their diverse functional roles (Table 1).

Table 1. The major functions, localization, and physiological significance of dopamine D1, D2, D3, D4, and D5 receptors in the brain.

Subtypes		Location	Responses	Ref.
D1-Like Receptors	D1 (D1A and D1B) Receptor	Predominantly in the striatum, nucleus accumbens, substantia nigra, olfactory bulb, and cortex	Stimulates adenylate cyclase, increasing intracellular cAMP levels	[1–3,5,6,13–19]
	D5 Receptor	Broadly distributed in the brain, including in the hippocampus, thalamus, striatum, nucleus accumbens, and amygdala	Stimulates adenylate cyclase, increasing intracellular cAMP levels	[1,4,5,20–23]
D2-Like Receptors	D2 (D2S and D2L) Receptor	Predominantly in the striatum, nucleus accumbens, and olfactory bulb; the hippocampus, amygdala, hypothalamus, and cortex at a lower level	Inhibits adenylate cyclase, decreasing cAMP levels	[6–10,24–34]
	D3 Receptor	Found in the nucleus accumbens, insular cortex, amygdala, and hippocampus	Inhibits adenylate cyclase, decreasing cAMP levels	[35–51]
	D4 Receptor	Located in the prefrontal cortex, hippocampus, amygdala, and striatum	Inhibits adenylate cyclase, decreasing cAMP levels	[52–58]

D1 receptors are predominantly abundant in the striatum, nucleus accumbens, the substantia nigra pars reticulata, the olfactory bulb, and cortex [1–3,5,6,13,14]. In contrast, D2 receptors, with the variants D2 short type (D2S) and D2 long type (D2L), are distributed in various brain regions [6–10,59,60], including the striatum, nucleus accumbens, and olfactory tubercle at a high density, and in the hippocampus, amygdala, hypothalamus, and cortical regions to a lower extent [31–34]. Dopamine D2L receptors are primarily found postsynaptically, but are also localized in the presynaptic terminal [33], which are abundantly expressed in areas of the brain associated with motor control, such as the striatum and substantia nigra [8,61,62]. Postsynaptic D2L receptors play a key role in inhibiting cAMP production when dopamine binds. This inhibition is associated with a reduction

in neuronal excitability. In contrast, D2S receptors are found both presynaptically on the neuron releasing dopamine, and postsynaptically. The presynaptic D2S receptor acts as an autoreceptor [33,63–65]. When dopamine binds to D2S receptors on presynaptic neurons, it inhibits further dopamine release, acting as a feedback mechanism [33,63,65]. These autoreceptors are found on the soma and dendrites of mesencephalic dopaminergic neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA), as well as on their axon terminals in projection areas, including striatum and nucleus accumbens [31,34]. Interestingly, D2S receptors are predominantly localized at the plasma membrane, whereas D2L receptors are also observed in the perinuclear region around the Golgi apparatus, and only D2L receptors have the ability to bind type 3 fatty acid-binding proteins (FABP3) [66]. Dopamine D3 receptors are prominent in the nucleus accumbens, insular cortex, amygdala, and hippocampus [37,38,67]. In contrast, D4 receptors are found in the prefrontal cortex, hippocampus, amygdala, and striatum [52–54]. D5 receptors are mainly found in the hippocampus, thalamus, striatum, nucleus accumbens, and amygdala [1,4,5,67].

The endocytic mechanism strictly regulates the number of dopamine D1–D5 receptors on the cell membrane in order to regulate dopaminergic signal transduction. Endocytosis can reduce the number of available receptors on the cell membrane via desensitization, thus decreasing the sensitivity of the cell to dopamine stimulation [68,69]. Endocytosis can also facilitate the recycling of receptors back to the cell membrane through resensitization, thus restoring the responsiveness of the cell to dopamine stimulation [68,69]. Endocytosis can furthermore modulate the signaling output of dopamine receptors by altering their interactions with other proteins, such as G proteins, in different endocytic compartments [68–70]. D1-like and D2-like dopamine receptors have different endocytic behaviors and responses to dopamine or drugs. For example, D1-like (D1 and D5) receptors are more resistant to endocytosis than D2-like (D2, D3, and D4) receptors, and they require higher concentrations of dopamine or longer stimulation times to be internalized [68,69]. D2-like receptors are also more sensitive to the effects of β-arrestins, which are proteins that bind to activated G protein-coupled receptors and promote their endocytosis and desensitization [68–70]. These data suggest that endocytosis is an important regulator of dopamine receptor signaling and function, and can have implications pertaining to various physiological and pathological processes.

3. Genetic Variants in Dopamine Receptors and Their Impacts on Neuropsychiatric and Movement Disorders

Genetic variants of dopamine receptors, especially single nucleotide polymorphisms (SNPs), have been extensively studied in terms of their association with various neuropsychiatric and neurodegenerative disorders, such as schizophrenia, bipolar disorder, addiction, Alzheimer's disease, and Parkinson's disease [71,72]. The effects of these variants may depend on the receptor subtype, the brain region, the disease phenotype, and the interaction with other genes and environmental factors. According to the D1 receptor, an SNP in the DRD1 gene (rs4532) has been linked to cognitive impairment and reduced prefrontal cortex activity in schizophrenia patients [67]. Another SNP (rs686) has been associated with an increased risk of heroin dependence [73,74]. In contrast, several SNPs in the D2 receptor named the DRD2 gene have been implicated in modulating the response to antipsychotic drugs, such as clozapine and risperidone [75]. A common variant (Taq1A) has been related to reduced D2 receptor density in the striatum, and increased susceptibility to addiction and Parkinson's disease pathogenesis [71].

A functional SNP in the D3 receptor, the DRD3 gene (Ser9Gly), has been shown to influence the affinity of the D3 receptor for dopamine and the efficacy of antipsychotic treatment [76]. This variant has also been associated with Parkinson's disease, especially in patients with cognitive impairment or psychosis [67]. Furthermore, genetic mutations of dopamine D2 and D3 receptors are associated with the pathogenesis of particular antipsychotics (AP)-induced parkinsonism, and dopamine D1, D2, and D3 receptor mutations affect the AP-induced tardive dyskinesia in patients with schizophrenia, respectively [72].

In the D4 receptor, a variable number tandem repeat (VNTR) polymorphism in the DRD4 gene, which affects the length of the third intracellular loop of the receptor, has been linked to various behavioral and personality traits, such as novelty seeking, impulsivity, and attention-deficit hyperactivity disorder [77]. This polymorphism may also modulate the response to methylphenidate, a dopamine reuptake inhibitor [78]. Concerning the D5 receptor, an SNP in the DRD5 gene has been reported to influence the expression of the D5 receptor in the brain and the susceptibility to schizophrenia [79]. Another SNP (rs1800762) has been associated with cognitive performance and working memory in healthy subjects and schizophrenia patients [71].

These findings suggest that genetic variants of dopamine D1, D2, D3, D4, and D5 receptors significantly affect the function and regulation of dopaminergic neurotransmission, and may contribute to the pathophysiology and treatment of various neurological and psychiatric disorders. Consequently, the functional significance of dopamine receptors spans motor control, reward, mood, attention, and cognitive processes. Therefore, based on the dopamine receptor subtypes and their distribution summarized in this paragraph, the following context from Section 5 will demonstrate the physiological functions of dopamine receptors and their relevance to neurodegenerative diseases categorized by major neuronal nuclei, as well as the pathophysiological significance of dopamine receptors in conditions characterized by dopaminergic dysregulation, such as Parkinson's disease, schizophrenia, and addiction.

4. Dopamine Receptor Imaging and Disease Implications in Humans

Dopamine receptor imaging is a technique that uses positron emission tomography (PET) or single-photon emission computed tomography (SPECT) to measure the density, distribution, and occupancy of dopamine receptors in the living human brain. Dopamine receptor imaging can provide valuable information on the function and dysfunction of the dopamine system in various neurological and psychiatric disorders, such as Parkinson's disease, schizophrenia, addiction, and cognitive impairment. Dopamine receptor imaging can also be used to assess the pharmacological effects and optimal dosing of drugs that target dopamine receptors, such as antagonists or partial agonists. Several radiotracers have been developed and validated for dopamine receptor imaging.

[^{11}C]SCH23390 and [^{18}F]fallypride are radioligands that bind to D1 receptors, which are mainly expressed in the striatum and the prefrontal cortex, and which are involved in motor and cognitive functions. [^{11}C]SCH23390 is a selective D1 receptor antagonist [18,19], while [^{18}F]fallypride is a non-selective D2/D3 receptor antagonist that can also bind to D1 receptors with a lower affinity [80,81]. [^{11}C]SCH23390 can be used to measure the D1 receptor density and occupancy in different brain regions, and to investigate the role of D1 receptors in various neurological and psychiatric disorders, such as schizophrenia, Parkinson's disease, and aging [18,19], which revealed the aging impact on D1 expression and the relation to motor decline in human [19].

Furthermore, [^{11}C]raclopride and [^{18}F]fallypride are non-selective radioligands that bind to both D2 and D3 receptors, and are commonly used to measure the receptor density and occupancy in the striatum and other brain regions. [^{11}C]raclopride is a D2/D3 receptor antagonist with more affinity for D2 receptors [82], while [^{18}F]fallypride is a D2/D3 receptor antagonist with similar affinity for both receptors [81], which visualizes the modified D2/D3 receptor density in a mouse model of Huntington's disease [80]. These radioligands can be used to study the dopamine system in various neuropsychiatric disorders, such as schizophrenia, Parkinson's disease, addiction, and cognitive impairment.

In contrast, [^{11}C]PHNO is a radioligand that binds to D3 receptors [50,83]. [^{11}C]PHNO is a selective D3 receptor agonist, and it can be used to measure the D3 receptor density and occupancy in different brain regions, showing the primary distribution in the hypothalamus, substantia nigra, globus pallidus, thalamus, and ventral striatum [50,83], are involved in reward, motivation, and emotion processes, and can be utilized to study the role of D3 receptors in various neuropsychiatric disorders, such as addiction, schizophrenia, and depression [51]. Based on these human clinical findings, the distribution and function of

dopamine receptors in each brain nucleus and their involvement in certain diseases will be discussed in the following sections.

5. Physiological Functions of Striatum Dopamine Receptors and Pathogenic Implications

5.1. Impact of Dopamine Receptors in the Dorsal Striatum (Caudate Nucleus and Putamen)

The basal ganglia, another basal nuclei, is an essential neuronal circuit for motor movement, emotion, learning, and cognition. The major components of the basal ganglia include the striatum, consisting of both the dorsal striatum (caudate nucleus and putamen) and the ventral striatum (nucleus accumbens and olfactory tubercle), the globus pallidus, the substantia nigra, and the subthalamic nucleus. The dorsal striatum consists of the putamen, which controls motor functions, and the caudate nucleus, which controls mental functions [84–86]. The caudate-putamen is a crucial component of the basal ganglia and involves various essential functions, including motor control, reward processing, and cognitive functions [86–90]. It primarily comprises two subtypes of neurons: the γ-aminobutyric acid (GABAergic) medium-sized spiny neurons (MSNs) in 95% and other interneurons in rodents [85]. Within this dynamic neural nucleus, both D1- and D2-like dopamine receptor subtypes orchestrate indispensable functions, with alterations in their equilibrium implicated in neurodegenerative and neuropsychiatric pathologies, such as Parkinson's disease, Huntington's disease, schizophrenia, and addiction [2,36,91–93]. Here, we elucidate the physiological significance of D1 and D2 receptors in the striatum, unraveling their distinctive roles in different receptor subtypes.

First, dopamine D1 receptors find predominant expression on the surface of direct pathway medium spiny neurons (dMSNs) [94–96]. Their physiological importance spans a spectrum, encompassing the facilitation of movement, reward and reinforcement, cognitive functions, and neuroplasticity. The activation of D1 receptors heightens the excitability of dMSNs, instigating and facilitating the execution of motor functions. These receptors are also integral for the perception of rewarding stimuli, reinforcing behaviors associated with positive outcomes. Striatal D1 receptors contribute to cognitive functions, including working memory, cognitive flexibility, and executive functions [16,94,97,98]. Notably, their stimulation fosters synaptic plasticity, influencing learning and memory processes within the striatum (Table 2).

Table 2. The distribution and major functions of dopamine D1–D5 receptors in the dorsal striatum and their implications for disorders.

Subtypes	Expression	Function	Related Diseases	Ref.
D1 receptors	Direct pathway medium spiny neurons (dMSNs)	Facilitation of movement, reward and reinforcement, cognitive functions, neuroplasticity	Motor disorders, including Parkinson's disease, Huntington's disease, schizophrenia, addictions	[5,13,36,84,85,93,95,96,99–102]
D2 receptors	Indirect pathway medium spiny neurons (iMSNs)	Inhibition of movement, modulation of reward, neurotransmitter release, motor learning	Motor disorders, including Parkinson's disease, Huntington's disease, schizophrenia, addictions	[9,36,84,85,91,93,95,96,99–106]
D3 receptors	Cholinergic interneurons and iMSNs	Emotional responses, motivation, cognitive functions	Addiction, schizophrenia, mood disorders	[36,38,46,83–85,99–101,107]
D4 receptors	GABAergic interneurons and dMSNs	Executive functions, emotional processing, response to novelty	Attention-deficit hyperactivity disorder (ADHD), certain psychiatric conditions	[36,53,54,84,85,99,101,104]
D5 receptors	Cholinergic and parvalbumin-positive interneurons, dMSNs	Modulation of motor activity and cognitive processes	Schizophrenia, cognitive dysfunction	[5,9,23,84,85,99,101]

In contrast, dopamine D2 receptors prominently inhabit the surface of indirect pathway medium spiny neurons (iMSNs) [95,96]. Their physiological role spans the inhibition of movement, the modulation of reward and neurotransmitter release, and the facilitation of motor learning. The activation of D2 receptors inhibits the activity of iMSNs, thereby curtailing the initiation and execution of movement. D2 receptor activation is pivotal in aversion processing and the modulation of responses to negative stimuli, thus contributing a counterbalance to reward-related behaviors. D2 receptors, residing on presynaptic terminals, intricately regulate dopamine release, thereby modulating the overall dopamine concentration in the striatum [26,27,90,108]. Furthermore, D2 receptors play a significant role in motor skill learning and adaptive processes (Table 2).

Dopamine D2 receptors are not only expressed by GABAergic MSNs in the striatum, but also by cholinergic interneurons (CINs), which constitute a small but important population of striatal neurons that release acetylcholine and modulate the activity of MSNs and other striatal cell types [109–112]. Dopamine D2 receptors in CINs have been shown to regulate the excitability and firing patterns of these neurons, as well as their synaptic interactions with dopaminergic and glutamatergic inputs [110,111]. For instance, the activation of D2 receptors in CINs can reduce their autonomous activity and induce a pause in their firing, which may facilitate the detection and processing of salient stimuli and behavioral responses [111]. Conversely, the blockade of D2 receptors in CINs can increase their firing rate and impair their ability to pause. Moreover, D2 receptors in CINs can modulate the release of acetylcholine in the striatum, which can in turn affect the function of other dopamine receptors, such as D1 and D5 receptors, on MSNs and CINs [111]. Therefore, D2 receptors in CINs may play a crucial role in the fine-tuning of striatal output and dopamine signaling, and may be involved in several aspects of disease. For example, the dysregulation of D2 receptors in CINs may contribute to the pathophysiology of schizophrenia, Parkinson's disease, and addiction, as these disorders are associated with altered dopamine transmission and impulsive choice behavior [110–112].

Maintaining an intricate balance between D1 and D2 pathway activities is imperative for proper motor control and cognitive functions [52,67,84,101,107,113–117]. Perturbations in this delicate equilibrium can lead to motor dysfunction, cognitive impairment, and alterations in reward processing. Imbalances in D1 and D2 signaling are notably associated with a spectrum of neurological and neuropsychiatric disorders, including Parkinson's disease, schizophrenia, and addiction. These data indicate that the nuanced interplay of D1 and D2 receptors in the striatum regulates motor control, cognitive processes, and the pathophysiology of diverse neurological and neuropsychiatric disorders (Table 2).

Other dopamine receptors, namely D3, D4, and D5 subtypes, exhibit distinct expression patterns and exert intricate influences on brain function [23,38,46,53,54]. D3 receptors, primarily situated in the limbic areas of the striatum, orchestrate emotional responses, motivation, and cognitive functions upon activation. The dysregulation of D3 receptors is strongly linked to addiction, schizophrenia, and mood disorders. In the prefrontal cortex and striatum, D4 receptors play a pivotal role in executive functions, emotional processing, and responses to novelty, with aberrant function being associated with ADHD and specific psychiatric conditions. D5 receptors, widely distributed throughout the brain, contribute significantly to the modulation of both motor activity and cognitive processes. Altered D5 receptor function is implicated in conditions such as schizophrenia and cognitive dysfunction (Table 2). Collectively, these data underscore the pathogenic impact of dopamine receptor subtypes in the striatum on neurological and neuropsychiatric disorders. Imbalances in or the dysregulation of these receptors emphasize the need for targeted therapeutic strategies to restore proper dopaminergic signaling for effective clinical interventions.

5.2. Impact of Dopamine Receptors in the Ventral Striatum (Nucleus Accumbens and Olfactory Tubercle)

The nucleus accumbens and the olfactory tubercle are part of the ventral striatum in the brain [118]. The ventral striatum is involved in processing sensory information, such

as olfactory and reward-related information [118–120]. The nucleus accumbens, a part of the structure called the striatum, is influenced by neurotransmitters such as dopamine and serotonin. It plays a significant role in behaviors related to pleasure, motivation, decision making, and addiction. On the other hand, the olfactory tubercle is a part of the structure called the olfactory cortex, and receives input from the olfactory epithelium. Apart from olfaction, the olfactory tubercle can integrate sensory information from other senses, such as hearing and vision. This is believed to influence social behavior and emotion.

In the nucleus accumbens, all D1 to D5 receptors are expressed, with D1 and D2 receptors being the most prevalent [1,6,14,36,52,107,117,121,122]. The D1 receptors are mainly localized in the direct pathway of medium spiny neurons, while D2 receptors are primarily found in the indirect pathway of medium spiny neurons. The activation of D1 receptors is believed to be involved in reward, motivation, and learning. Conversely, the activation of D2 receptors is associated with reward, pleasure, and addiction. D3 receptors are predominantly located in the shell of the nucleus accumbens, and are implicated in fear, anxiety, and depression. D4 receptors are mainly found in the core of the nucleus accumbens, and are thought to be involved in psychiatric disorders such as ADHD and schizophrenia. D5 receptors, localized in the shell of the nucleus accumbens and the olfactory tubercle, are believed to play a role in memory and cognition (Table 3).

Table 3. The distribution and major functions of dopamine D1–D5 receptors in the ventral striatum (nucleus accumbens and olfactory tubercle) and their implication for disorders.

Subtypes	Expression	Function	Related Diseases	Ref.
D1 receptors	Predominantly in the dMSNs	Rewards, motivation, and learning; olfaction and learning	Implicated in addiction, ADHD, schizophrenia, and depression	[1,6,14,36,52,85,99,100,106,107,117,121,122]
D2 receptors	Predominantly in the iMSNs	Rewards, pleasures, and addictions; olfaction, social behavior, and emotion	Linked to Parkinson's disease, addiction, schizophrenia	[1,6,14,36,52,85,99,100,106,107,117,121,122]
D3 receptors	Nucleus accumbens shell; large aspiny neuron	Fear, anxiety, and depression; olfaction and rewards	Associated with addiction, depression, and schizophrenia	[83,85,99,100,107,121]
D4 receptors	Nucleus accumbens core; medium aspiny neuron	Attention and motivation; olfaction and attention	Linked with ADHD and schizophrenia	[53,54,85,99,100,121]
D5 receptors	Nucleus accumbens shell; dMSNs	Memory and cognition; olfaction and memory	Implicated in learning, memory, and cognitive disorders	[23,85,99,100,121]

In contrast, all D1 to D5 receptors are expressed in the olfactory tubercle, with D2 receptors being the most abundant [1,6,14,36,106,121,122]. D2 receptors are primarily localized in the indirect pathway of medium spiny neurons. The activation of D2 receptors is believed to be involved in olfaction, social behavior, and emotion. D1 receptors are mainly found in the direct pathway of medium spiny neurons; D3 receptors are predominantly in large aspiny neurons; D4 receptors are mainly found in medium aspiny neurons; and D5 receptors are primarily localized in the direct pathway of medium spiny neurons. The activation of D1 receptors is considered to be involved in olfaction and learning. The activation of D3 receptors is thought to be associated with olfaction and reward. The activation of D4 receptors is believed to be related to olfaction and attention. The activation of D5 receptors is considered to be involved in olfaction and memory (Table 3). Dopamine D2 receptors in the ventral striatum are not only expressed by GABAergic MSNs, but also by CINs.

Despite the heterogeneous distribution of D1- and D2-like dopamine receptors across the brain, it is noteworthy that these receptors can be expressed on the same type of neurons. Recent findings regarding the modulation of dopamine receptor signaling

in striatal neurons reveal pivotal molecular insights, particularly alterations linked to addiction and dyskinesia [15,123,124]. Furthermore, studies comparing the affinities of drugs targeting dopamine receptor subtypes D1, D2, and D3 underscore the potential therapeutic avenues for treating schizophrenia, bipolar disorder, and depression [125]. Notably, investigations into the activation of the D1–D2 receptor complex demonstrate promising outcomes in curbing cocaine-seeking behaviors in animal models, indicating novel signaling pathways involving Gq/phospholipase C (PLC)/protein kinase C (PKC) signaling [126]. In addition to dopamine D1 receptors, the modulation of D2 receptor-dependent Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and the extracellular signal-regulated kinases (EKR) signaling pathway can alleviate cocaine-induced conditioned place preference (CPP) [127–129].

In addition, both MSNs and CINs express dopamine D2 and D3 receptors in the nucleus accumbens [130–132]. D2 and D3 receptors have different affinities for dopamine, with D3 receptors having a higher affinity than D2 receptors. Therefore, D3 receptors may be more sensitive to low dopamine levels, while D2 receptors may be more responsive to high dopamine levels. Moreover, D2 and D3 receptors can form heterodimers with each other or with other dopamine receptors [130,131,133,134], such as D1 and D3 receptors [133–135]. The co-expression and heterodimerization of D2 receptors and D3 receptors in the nucleus accumbens may distinctly and specifically contribute to the regulation of reward-related behaviors and the development of addiction and other neuropsychiatric disorders [133,134]. For instance, the D2 receptor and D3 receptor in MSNs may differentially modulate the activity and plasticity of the direct and indirect pathways, which have opposite effects on motor output and reward processing. D2 receptors and D3 receptors in CINs may differentially regulate the release of acetylcholine in the nucleus accumbens, which can, in turn, affect the function of other dopamine receptors on MSNs and CINs. The dysregulation of D2 and D3 receptor signaling in the nucleus accumbens may lead to the dysfunction and degeneration of nucleus accumbens neurons and circuits, impairing reward-related learning and decision making [130–134].

Together, these advances underscore the potential of targeted receptor modulation in addressing addiction and neuropsychiatric conditions, offering novel insights and potential therapeutic approaches which target the ventral striatum dopamine receptors.

6. Impact of Dopamine Receptors in the Prefrontal Cortex

The prefrontal cortex represents a pivotal brain region which orchestrates a spectrum of cognitive processes, including executive functions, decision making, emotional regulation, and working memory [136]. Its intricate interplay with the basal ganglia forms the crux of sophisticated neurobehavioral operations, marked by a complex network of parallel loops that underpin diverse physiological functions. Central to this interaction, the prefrontal cortex establishes glutamatergic connections to the striatum, the principal input nucleus of the basal ganglia. Herein, the striatum adeptly integrates a convergence of cortical inputs with dopaminergic innervation stemming from the substantia nigra pars compacta and the ventral tegmental area. Following this integration, the striatum dispatches inhibitory projections to the output structures of the basal ganglia, namely the globus pallidus and the substantia nigra pars reticulata. These output structures govern thalamic activity, modulating the excitatory output that, in a reciprocal loop, is projected back to the prefrontal cortex. This intricate circuitry forms a comprehensive loop involving cortical-striatal-thalamic-cortical pathways, constituting the basis of higher-order cognitive and motor functions. Dopamine receptors in the prefrontal cortex, particularly the D1 and D2 receptor subtypes, play significant roles in these processes.

In detail, dopamine D1 receptors are primarily expressed on the excitatory pyramidal neurons in the prefrontal cortex [121,137,138]. The activation of D1 receptors is associated with improved working memory, cognitive flexibility, and attention. It enhances the strength of excitatory synapses and facilitates the neural circuits responsible for executive

functions. The dysfunction of D1 receptors in the prefrontal cortex has been implicated in cognitive disorders such as ADHD and schizophrenia (Table 4).

Table 4. The distribution and major functions of dopamine D1–D5 receptors in the prefrontal cortex and their implication for disorders.

Subtypes	Physiological Functions	Related Diseases	Ref.
D1 receptors	Working memory maintenance, cognitive flexibility, executive functions, modulation of emotional responses	Implicated in cognitive deficits, schizophrenia	[38,67,85,88,99,100,118–120,125,139]
D2 receptors	Modulation of executive functions, inhibition of impulsive behavior, regulation of reward-related behaviors, influences on attention and motivation	Associated with ADHD, addiction, cognitive impairments	[38,67,85,88,99,100,118–120,125,139]
D3 receptors	Modulation of emotional responses, involvement in motivation and reward, potential role in addiction and dependence	Implicated in mood disorders, addiction	[38,67,85,88,99,100,118–120,125]
D4 receptors	Contribution to executive functions, role in emotional processing, response to novelty, implications in attention disorders	Linked to ADHD, psychiatric impairments	[67,85,88,99,100,118–120,125]
D5 receptors	Modulation of cognitive processes, potential involvement in schizophrenia	Associated with cognitive impairments, schizophrenia	[5,23,84,121]

On the other hand, dopamine D2 receptors in the prefrontal cortex are expressed on both excitatory pyramidal neurons and inhibitory interneurons [8,26,29,140–142]. The activation of D2 receptors is generally associated with inhibitory neurotransmission. D2 receptors modulate the balance of excitation and inhibition in the prefrontal cortex, influencing working memory and decision-making processes. Importantly, in the striatum, where D2 receptors are mainly expressed by GABAergic MSNs and CINs, D2 receptor activation preferentially induces G protein signaling, which modulates the activity and plasticity of MSNs, and affects motor and reward-related behaviors [143–146]. However, in the prefrontal cortex, where D2 receptors are mainly expressed by glutamatergic pyramidal neurons, D2 receptor activation preferentially induces β-arrestin signaling, which modulates the trafficking and stability of D2 receptors, and affects cognitive and emotional functions [144,147,148]. These variations in receptor signaling may underlie differences in physiological functions and contribute to distinct disease conditions. Indeed, the dysregulation of D2 receptor signaling in these brain regions may be involved in the pathophysiology of various neuropsychiatric disorders, such as schizophrenia [149] (Table 4), while the dysregulation of striatal D2 receptors contributes to addiction [145,146] (Table 2).

The D3 receptors, known for their modulation of emotional responses and involvement in motivation and reward circuits, have been implicated in addiction and dependence [38,42,43,46,49]. Their dysregulation is closely associated with mood disorders and addictive behaviors, illuminating their significant role in these conditions. Conversely, the D4 receptors contribute substantially to executive functions, emotional processing, and responses to novelty [53,54,150–152]. Their implications in attention disorders, especially attention-deficit hyperactivity disorder (ADHD), and certain psychiatric impairments underscore their role in cognitive and behavioral functions. Additionally, D5 receptors, which modulate cognitive processes and have been tentatively linked to schizophrenia, are associated with cognitive impairments and the development of schizophrenia (Table 4).

These data suggest that dopamine receptors in the prefrontal cortex play a crucial role in regulating cognitive functions, and imbalances or dysfunctions in these receptors can contribute to the pathogenesis of cognitive disorders. Understanding the intricate role of dopamine in the prefrontal cortex is essential for developing targeted therapeutic interventions for cognitive-related conditions.

7. Impact of Dopamine Receptors in the Subthalamic Nucleus

The subthalamic nucleus is a critical part of the basal ganglia circuitry, which is involved in sensory and motor control [153–155]. While the presence of dopamine receptors, particularly D1–D5, has been identified, their specific roles and implications in disorders within this specific region are not yet fully elucidated. Parkinson's disease, characterized by dopaminergic neuron degeneration in the substantia nigra, impacts the basal ganglia circuitry, including the subthalamic nucleus, which has implications for motor symptoms and related dysfunctions [13,102,113,117,156–158]. Dopamine receptors in the subthalamic nucleus also play a crucial role in modulating the release of hormones from the hypothalamus, thereby influencing the endocrine system. Dopamine receptors in the hypothalamus have a physiological significance in hormone regulation, temperature regulation, and appetite and weight regulation.

Dopamine D1 receptors in the subthalamic nucleus modulate thalamocortical activity, impacting motor functions, the regulation of neuronal activity, working memory, and cognitive flexibility. Dysregulation in D1 receptors is linked to movement disorders such as Parkinson's disease, dyskinesia, schizophrenia, and addiction. D2 receptors regulate thalamic output, reward processing, and motor control, and their dysfunction is associated with schizophrenia, Parkinson's disease, addiction, and depression. D3 receptors mediate thalamic inhibition, motivation, and emotional regulation, and are implicated in schizophrenia, addiction, depression, and anxiety. D4 receptors influence thalamic gating, novelty seeking, and impulsivity, and their dysfunction is implicated in schizophrenia, ADHD, and addiction. D5 receptors enhance thalamocortical transmission, learning, and memory, and their implication extends to schizophrenia, Parkinson's disease, and Alzheimer's disease (Table 5).

Table 5. The distribution and major functions of dopamine D1–D5 receptors in the subthalamic nucleus and their implication for disorders.

Subtypes	Physiological Functions	Related Diseases	Ref.
D1 receptors	Modulation of thalamocortical activity; motor functions, regulation of neuronal activity, working memory, and cognitive flexibility	Linked to movement disorders such as Parkinson's disease, dyskinesia, schizophrenia, and addiction	[13,14,102,117,122,156,158]
D2 receptors	Regulates thalamic output; reward processing and motor control	Associated with schizophrenia, Parkinson's disease, addiction, depression	[14,102,113,122,157,159,160]
D3 receptors	Mediates thalamic inhibition, motivation, and emotional regulation	Implications in schizophrenia, addiction, depression, anxiety	[42,83,100,107,161,162]
D4 receptors	Influences thalamic gating, novelty seeking, and impulsivity	Implications in schizophrenia, ADHD, addiction	[67,150,155,163]
D5 receptors	Enhances thalamocortical transmission, learning, and memory	Implication in schizophrenia, Parkinson's disease, Alzheimer's disease	[20,67,155,156,163]

Furthermore, dopamine receptors in the hypothalamus are also involved in regulating hormone release, including the inhibition of prolactin secretion—a hormone which is crucial for lactation and reproductive functions [31]. Both D1 and D2 receptors may participate in the modulation of hormone release. Dopamine in the hypothalamus also

contributes to the regulation of body temperature, influencing thermoregulatory responses. Additionally, dopamine signaling in the hypothalamus is implicated in regulating appetite and body weight, and disruptions in this system may contribute to conditions like obesity. The dysfunction of dopamine receptors in the hypothalamus is linked to the loss of biological homeostasis, potentially leading to disorders of hormone secretion and reproductive system-related conditions. Altered dopamine signaling may also contribute to temperature dysregulation and issues such as hyperthermia or hypothermia. Dysfunction in the dopaminergic system in the hypothalamus has been implicated in disorders related to appetite and weight, including obesity or eating disorders. These data suggest that dopamine receptors in the hypothalamus are crucial for endocrine regulation, metabolism, and related physiological functions.

Therefore, dopamine receptors in the limbic system contribute significantly to motor regulation and hormone secretion. The dysregulation of these receptors is linked to various neuropsychiatric disorders, emphasizing their importance as potential targets for therapeutic interventions. Understanding the nuanced roles of dopamine receptors in these brain regions is crucial for developing targeted treatments for conditions affecting emotional and cognitive functions.

8. Impact of Dopamine Receptors in the Limbic System

8.1. Impact of Dopamine Receptors in the Amygdala

Dopamine receptors in the limbic system, encompassing structures like the amygdala and hippocampus, are integral for emotional processing, memory formation, and reward-related behaviors [3,14,102,107,117,121,122,158,164,165]. The limbic system is a complex network of brain structures that play a crucial role in regulating emotions, memory, and certain autonomic functions. It includes several interconnected regions located in the cerebral cortex and subcortical areas. Pivotal structures within the limbic system include the hippocampus, amygdala, hypothalamus, thalamus, and cingulate gyrus. The limbic system interacts with other brain regions to modulate emotional responses, store and retrieve memories, and regulate physiological processes associated with the stress response. Dysfunction in the limbic system is implicated in various psychiatric and neurological disorders, including mood disorders, anxiety disorders, and memory-related conditions.

The amygdala, with its intricate connections and roles in emotional regulation and fear conditioning, is impacted by dopamine signaling through various receptor subtypes. In the amygdala, both D1 and D2 receptor subtypes are expressed [67,164,166]. The activation of D1 receptors is linked to the modulation of emotional responses, fear learning, and the consolidation of emotional memories. On the other hand, D2 receptor activation in the amygdala is associated with the regulation of anxiety and stress responses [28,38,166]. Dysregulation in dopamine receptor expression or function within the amygdala has been associated with various mood disorders, anxiety disorders, and conditions, involving emotional dysregulation (Table 6).

In contrast, dopamine D3 receptors in the amygdala are implicated in the modulation of emotional responses, motivation, and reward processes, potentially contributing to addiction and dependence. They are suggested to have associations with mood disorders, addictive behaviors, and anxiety disorders. Meanwhile, D4 receptors contribute to emotional processing and play a role in responding to novelty, impacting attention and cognitive tasks. They have been linked to attention-deficit hyperactivity disorder (ADHD), schizophrenia, and depression. Furthermore, D5 receptors modulate emotional responses and are involved in cognitive processes, thus potentially influencing schizophrenia. These receptors have been associated with Alzheimer's disease, depression, and drug abuse (Table 6).

Table 6. Major functions of dopamine D1–D5 receptors in the amygdala and their implication for disorders.

Subtypes	Physiological Functions	Related Diseases	Ref.
D1 receptors	Modulation of emotional responses, fear conditioning, synaptic plasticity Facilitates neuronal plasticity, which is necessary for fear conditioning and fear elimination	Dysfunctions linked to mood disorders, anxiety, and fear-related pathologies	[3,14,57,117,121,122,158,164, 166,167]
D2 receptors	Regulation of emotional responses and reinforcement learning Suppresses neuronal plasticity, which is necessary for fear conditioning and fear elimination	Altered expression associated with mood disorders, addictive behaviors, anxiety	[14,28,38,57,122,166,167]
D3 receptors	Modulation of emotional responses, motivation, and reward, potential role in addiction and dependence	Potential involvement in mood disorders, addictive behaviors, anxiety disorders	[38,41,57,67,83,107,168]
D4 receptors	Contribution to emotional processing, role in response to novelty, implications in attention and cognitive tasks	ADHD, schizophrenia, depression	[55,57,67,169]
D5 receptors	Modulation of emotional responses, involvement in cognitive processes, potential role in schizophrenia	Alzheimer's disease, depression, drug abuse	[23,57,121,164,167]

8.2. Impact of Dopamine Receptors in the Hippocampus

The hippocampus, a critical region for learning and memory, also expresses both D1- and D2-like receptors. Dopamine receptors, particularly the D1 and D2 subtypes, play crucial roles in synaptic plasticity, memory formation, and cognitive functions within the hippocampus [3,5,13,14,21,52,56,102,116,117,162]. Dysregulation or alterations in the expression of these receptors have been associated with various cognitive disorders, memory impairments, and neurodegenerative diseases. D1 receptor activation is involved in long-term potentiation (LTP), a cellular process crucial for memory formation. D2 receptors modulate synaptic plasticity and are involved in memory consolidation. Changes in dopamine receptor function in the hippocampus are associated with cognitive impairments seen in disorders such as Alzheimer's disease and schizophrenia (Table 7).

In contrast, dopamine D3 receptors in the hippocampus are involved in the modulation of synaptic transmission, and are suggested to play potential roles in hippocampal function. Their dysregulation has been associated with conditions such as schizophrenia, depression, and drug abuse. On the other hand, D4 receptors play a crucial role in modulating neurotransmitter release and receptor sensitivity, which are linked to neuronal development and plasticity. Disruptions in these receptors are implicated in attention-deficit hyperactivity disorder (ADHD), schizophrenia, and depression. Additionally, D5 receptors are responsible for activating the signaling pathways crucial for neuronal plasticity and learning. Dysfunctions in these receptors have been associated with Alzheimer's disease, depression, and drug abuse (Table 7).

In detail, the hippocampus receives dopaminergic innervation from the following two main sources: the ventral tegmental area (VTA) and the locus coeruleus (LC) [170–172]. The VTA provides direct dopaminergic projections to the hippocampus, while the LC provides indirect dopaminergic projections via noradrenergic neurons that co-release dopamine. However, the density and distribution of dopaminergic innervation in the hippocampus are relatively low and heterogeneous when compared to other brain regions, such as the striatum and the prefrontal cortex. Moreover, the dopaminergic innervation shows a dorsoventral gradient, with higher levels in the ventral hippocampus than in the dorsal hippocampus [170–172]. The low level of dopamine

innervation in the hippocampus may influence the relative roles of the dopamine receptors therein, which include D1, D2, D3, D4, and D5 receptors. These receptors are differentially expressed in the hippocampal subregions and cell types, and mediate the diverse effects impacting synaptic transmission, plasticity, and network activity.

For instance, D1 and D5 receptors are mainly located on the dendritic spines of pyramidal neurons and modulate glutamatergic excitatory inputs, while D2 and D3 receptors are mainly located on the axon terminals of GABAergic interneurons and modulate inhibitory inputs [170–172]. D4 receptors are more sparsely expressed, and they have complex effects on both excitatory and inhibitory transmission. The balance and interaction of these receptors may determine the optimal level of dopamine signaling for hippocampal function. The dysregulation of dopamine signaling in the hippocampus may lead to the dysfunction and degeneration of hippocampal neurons and circuits, and may impair hippocampus-dependent memory processes. Several studies have reported reduced levels of dopamine and dopamine receptors in the hippocampus of Alzheimer's disease patients and animal models, as well as altered dopamine-dependent synaptic plasticity and memory performance [93,173–175]. Moreover, some studies have suggested that the modulation of dopamine receptors may have therapeutic potential for Alzheimer's disease, as it may enhance hippocampal function and attenuate Alzheimer's disease-related symptoms [93,173–175]. These phenomena may contribute to the pathophysiology of Alzheimer's disease, a neurodegenerative disorder characterized by progressive cognitive decline and memory loss.

Table 7. Major functions of dopamine D1–D5 receptors in the hippocampus and their implication for disorders.

Subtypes	Physiological Functions	Related Diseases	Ref.
D1 receptors	Modulation of synaptic plasticity, long-term potentiation (LTP), memory formation	Alzheimer's disease, depression, drug abuse	[3,5,13,14,34,67,102,116,117,176]
D2 receptors	Regulation of synaptic transmission, modulation of neuronal excitability	Alzheimer's disease, depression, drug abuse	[14,34,67,116,176]
D3 receptors	Modulation of synaptic transmission, potential roles in hippocampal function	Schizophrenia, depression, drug abuse	[34,45,67,162,177]
D4 receptors	Modulates neurotransmitter release and receptor sensitivity related to neuronal development and plasticity	ADHD, schizophrenia, depression	[34,52,56,67,169]
D5 receptors	Activates signaling pathways required for neuronal plasticity and learning	Alzheimer's disease, depression, drug abuse	[20,21,34,67,176]

9. Impact of Dopamine Receptors in the Midbrain

9.1. Impact of Dopamine Receptors in the Substantia Nigra

The physiological significance of dopamine receptors in the substantia nigra (SN) and ventral tegmental area (VTA) is integral to the regulation of movement, reward, and motivation. Both regions are critical components of the dopaminergic system in the brain. The dysregulation of dopamine receptors in these areas is linked to various disorders. In Parkinson's disease, dopamine-producing neurons are degenerated in the SN, leading to motor impairments [91,101,178–183]. Dysfunctions in the VTA and associated reward pathways are implicated in addiction and mood disorders [184–187].

The substantia nigra, particularly its dopamine-abundant areas, plays a crucial role in motor control, reward mechanisms, and behavioral responses [15,67]. In the intricate orchestration of neurotransmission within the mesencephalic substantia nigra, dopamine

D1-like and D2-like receptors play pivotal roles, particularly in the modulation of GABA release to the globus pallidus via the striatum. Dopamine receptors, especially the D1 and D2 subtypes, are integral in regulating motor function and reward processing within this brain region. Dysregulation or alterations in the expression of these receptors are strongly associated with movement disorders, including Parkinson's disease, and could potentially contribute to other neuropsychiatric conditions.

In the SN, particularly the pars compacta, dopamine-producing neurons play a central role in controlling voluntary movement. In Parkinson's disease and dopa-responsive dystonia, particularly tyrosine hydroxylase, the rate-limiting enzyme for dopamine biosynthesis, is reduced; therefore, the strict regulation of dopamine receptors is crucial [182,188]. The activation of D1 receptors in the nigrostriatal pathway, particularly on the surface of the dMSNs, facilitates the initiation and execution of movement. These receptors enhance the excitability of GABAergic dMSNs to enhance GABA release to the internal segment of globus pallidus (GPi), resulting in the promotion of motor function [189–193].

Simultaneously, D2 receptors, predominantly expressed in the indirect pathway medium spiny neurons (iMSNs), exert inhibitory control over GABA release to the external segment of globus pallidus (GPe), which modulates the GPi through the subthalamic nucleus [189–193]. The interplay between the D1 and D2 receptor-mediated modulation of GABAergic transmission intricately regulates the output of the substantia nigra, influencing downstream motor circuits. The dysregulation or degeneration of dopamine-producing neurons in the pars compacta, leading to alterations in D1 and D2 receptor activation and GABA release, is a hallmark of Parkinson's disease. This results in motor symptoms such as tremors, rigidity, and bradykinesia (Table 8).

Table 8. Major functions of dopamine D1–D5 receptors in the substantia nigra (SN) and their implication for disorders.

Subtypes	Physiological Functions	Related Diseases	Ref.
D1 receptors	Positive modulation of motor coordination, influencing cognitive functions	Dysfunctions linked to movement disorders like Parkinson's disease, motor impairments, and potentially addictive behaviors	[15,22,84,93,101,125,189,191–194]
D2 receptors	Inhibition of excessive movement, control of reward-related behaviors involvement in motor skill learning	Altered expression associated with movement disorders, such as Parkinson's disease, and some neuropsychiatric conditions	[22,91,93,101,125,140,194,195]
D3 receptors	Modulation of emotional responses Regulation of cognitive functions	Potential implications in movement disorders	[38,42,49,83,101,125]
D4 receptors	Contribution to executive functions Role in response to novelty	Parkinson's disease, motor impairments	[53,54,67,84,101]
D5 receptors	Modulation of motor activity Regulation of cognitive functions	Parkinson's disease, motor impairments	[4,20,22,23,101]

Dopamine D3 receptors in SN play a role in modulating emotional responses and regulating cognitive functions, potentially having implications for movement disorders. On the other hand, D4 receptors contribute to executive functions and are involved in responding to novelty. Dysfunctions in these receptors are associated with Parkinson's disease and motor impairments. Additionally, D5 receptors are responsible for modulating motor activity and regulating cognitive functions. Aberrations in these receptors have been linked to Parkinson's disease and motor impairments (Table 8).

Parkinsonism is a typical phenotype of substantia nigra dysfunction. Parkinson's disease is characterized by a significant reduction in the levels of tyrosine hydroxylase, the rate-limiting enzyme in dopamine biosynthesis [196–200]. This reduction leads to a diminished capacity for dopamine synthesis, necessitating the precise regulation of dopamine

receptors [197,198,200]. Reduced dopamine production in parkinsonism results in the reduction of D1 receptor activation. This leads to a decrease in the excitability of dMSNs and a subsequent reduction in GABA release to GPi. The impaired excitatory input to the GPi contributes to motor symptoms like tremors, rigidity, and bradykinesia [201–203]. In contrast, D2 receptors exert inhibitory control over GABA release to GPe. The modulation of GABAergic transmission by D2 receptors is crucial for the delicate balance between the direct and indirect pathways [10,204]. In parkinsonism, alterations in D2 receptor activation disrupt this balance, contributing to the overall motor dysfunction observed in the disease. The intricate interplay between the D1 and D2 receptor-mediated modulation of GABAergic transmission intricately regulates the output of the substantia nigra, influencing downstream motor circuits. Furthermore, the compensatory enhancement of TH phosphorylation and dopamine D1 receptor expression alleviates motor dysfunction in order to mitigate the severity of hypokinesia [205]. These data imply that the dysregulation or degeneration of dopamine-producing neurons in the pars compacta leads to alterations in D1 and D2 receptor activation and GABA release, which is a hallmark of Parkinson's disease.

9.2. Impact of Dopamine Receptors in the Ventral Tegmental Area

On the other hand, VTA is a crucial brain region, containing dopaminergic neurons that project to various areas of the brain, including the nucleus accumbens and prefrontal cortex [185,206–209]. The physiological significance of dopamine receptors in the VTA is associated with regulating reward, motivation, reinforcement, and cognitive functions. D1 receptors in the VTA play a key role in the reward pathway. The activation of these receptors is involved in the experience of pleasure and the reinforcement of behaviors associated with positive outcomes. They contribute to the motivation one feels to seek rewards. The dysregulation of D1 receptor signaling in the VTA is implicated in reward processing and motivation disorders. This dysfunction is associated with conditions like addiction, where there is an aberrant reinforcement of drug-seeking behavior (Table 9).

Table 9. Major functions of dopamine D1–D5 receptors in the ventral tegmental area (VTA) and their implication for disorders.

Subtypes	Physiological Functions	Related Diseases	Ref.
D1 receptors	Regulation of reward-related behaviors, control of motivation and reinforcement, contribution to emotional responses	Dysfunctions may contribute to addictive behaviors, mood disorders, and cognitive impairments	[1,6,13,102,116,125,210–212]
D2 receptors	Modulation of aversive responses, regulation of neurotransmitter release, contribution to motor learning and adaptation	Altered expression linked to addiction, schizophrenia, and potentially motor-related disorders	[1,6,116,125,210,211]
D3 receptors	Influence on motivation and reward processing, potential role in drug addiction and dependence	Implications in addiction and reward-related disorders	[38,67,125,210]
D4 receptors	Involved in regulating dopamine pathways, potential role in motivation	Potential involvement in motivation and reward-related disorders, depression	[54,67,150,210,213]
D5 receptors	Modulates neurotransmission, influences motor functions and cognitive processes	Addiction and cognitive impairments, depression	[4,20,23,67,210]

In contrast, D2 receptors in the VTA are involved in modulating the response to rewarding and aversive stimuli. Their activation can inhibit dopamine release in target areas, thus contributing to the regulation of reward-related behaviors. Imbalances in

D2 receptor function in the VTA are associated with psychiatric conditions, including schizophrenia. Altered dopamine release and disrupted reward processing contribute to the symptomatology of these disorders. The activation of D2 receptors in the nucleus accumbens, which is the projection site of VTA dopaminergic neurons, is associated with the hedonic aspects of reward-related behaviors (Table 9).

Dopamine D3 receptors in VTA exert an influence on motivation and reward processing, potentially playing a role in drug addiction and dependence. Dysfunction in these receptors is implicated in addiction and reward-related disorders. D4 receptors are involved in regulating dopamine pathways, and may have a role in motivation, potentially contributing to motivation and reward-related disorders, as well as depression. Additionally, D5 receptors modulate neurotransmission, impacting motor functions and cognitive processes. Dysfunctions in these receptors are associated with addiction and cognitive impairments, along with depression (Table 9).

These data suggest that the physiological significance of dopamine receptors in the SN lies in their role to regulate motor function via the intricate balance of D1 and D2 receptor-mediated pathways. The pathogenic impact involves disruptions in this balance, leading to movement disorders like Parkinson's disease. In contrast, the physiological significance of dopamine receptors in the VTA lies in their central role in the brain's reward system. The pathogenic impact involves disruptions in reward processing, motivation, and reinforcement, contributing to the development of neuropsychiatric disorders.

10. Dopamine Receptors as Drug Targets

10.1. Dopamine D1-like Receptors as Therapeutic Targets

This review highlighted that the dopamine receptors in various brain nuclei are involved in diverse neuropsychiatric disorders, such as depression, schizophrenia, Parkinson's disease, and drug addiction. Therefore, they have been considered as potential therapeutic targets for the development of novel drugs. However, the complexity and diversity of dopamine receptor signaling, and pharmacology pose significant challenges for designing selective and effective ligands. As mentioned above, dopamine D1 receptors are mainly expressed in the striatum, stimulating the direct pathway and facilitating movement. They are also expressed in the prefrontal cortex, enhancing cognitive functions such as working memory, attention, and decision making. Because of the wide variety of functions and distributions, the development of clinically effective D1 receptor agonists has been challenging due to the lack of selectivity, bioavailability, and safety of the available compounds.

The exploration of D1/D5 receptor-selective partial agonists shows promise in providing sustained, predictable motor control, while reducing the risk of complications, presenting a potential shift in the classification of dopamine agonists based on their receptor selectivity [214]. High intrinsic activity D1 agonists could offer significant symptomatic relief, even in severe stages of the disease, potentially improving the quality of life for late-stage Parkinson's patients [215]. In recent years, several novel non-catecholamine D1 receptor agonists have been discovered, which demonstrate improved pharmacological properties and therapeutic potential. Non-catecholamine D1/D5 receptor agonists can dissociate Gs protein signaling from β-arrestin recruitment, and may be useful for treating motor impairment in Parkinson's disease and cognitive impairment in neuropsychiatric disorders [15,216]. For example, the dopamine D1 receptor potentiator DETQ [2-(2,6-dichlorophenyl)-1-((1S,3R)-3-(hydroxymethyl)-5-(2-hydroxypropan-2-yl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one] demonstrated significant allosteric effects in human D1 receptors, inducing a leftward shift in the cAMP response to dopamine [217]. DETQ increased locomotor activity in a dose-dependent manner in a knock-in mouse model expressing human D1 receptors [217]. In addition, PF-06649751, also known as tavapadon, is a partial agonist of the dopamine D1/D5 receptor [218–220]. PF-06649751 has been shown to improve motor function in Parkinson's disease [218–220]. PF-06649751 has a novel non-catechol structure, which may make it more selective and sta-

ble than other dopamine agonists [220]. PF-06412562 is also a partial agonist of dopamine D1 and D5 receptors, which are involved in motor functions [221–223]. PF-06412562 has been shown to improve motor deficits in Parkinson's disease with no serious adverse events, severe adverse events, or adverse events, although it did not improve cognitive function or motivation/reward processing [221]. Although clinical trials are challenging due to inadequate therapeutic efficacy and side effects [179], dopamine D1-like receptors remain a potential therapeutic target.

10.2. Dopamine D2-like Receptors as Therapeutic Targets

In contrast, dopamine D2 receptors are widely distributed in the brain, where they mediate diverse functions, such as reward processing, reinforcement learning, and motor coordination, as described above. While striatal D2 receptors were significantly decreased in PD patients when compared to a healthy control group and patients with Alzheimer's disease, combined densities of striatal D1 and D3 receptors showed better correlations with clinical manifestations of Parkinson's disease, suggesting potential implications for diagnosis, treatment, and prognosis, especially in elderly patients with low D2 receptors expression [224]. The majority of antipsychotic drugs target D2 receptors, as they block the excessive dopamine transmission that is associated with psychotic symptoms. However, these drugs also cause adverse effects, such as extrapyramidal symptoms, weight gain, and metabolic syndrome, due to their lack of specificity and their blockade of D2 receptors in other brain regions. Therefore, there is a need for more selective and efficacious D2 receptor modulators that can restore the optimal balance of dopamine signaling in different brain circuits.

Biased D2 receptor agonists can preferentially activate Gi protein or β-arrestin pathways, and may exert different effects on reward and aversion [34]. Moreover, allosteric modulators can modulate the affinity and efficacy of orthosteric ligands, and may provide more fine-tuned control over dopamine receptor signaling [225]. One approach is to develop D2 receptor partial agonists, which have lower intrinsic activity than full agonists, and can act as antagonists in the presence of high dopamine levels or agonists in the presence of low dopamine levels. Examples of D2 receptor partial agonists are aripiprazole and brexpiprazole, which are approved for the treatment of schizophrenia, bipolar disorder, and major depressive disorder [226,227]. Another approach is to develop D2 receptor allosteric modulators, which bind to a distinct site from the orthosteric site and enhance or inhibit the binding and efficacy of the endogenous ligand or other drugs. For instance, PAOPA is a positive allosteric modulator of D2 receptors, which increases the affinity and potency of dopamine and D2 receptor agonists, and reverses the motor and cognitive impairments induced by D2 receptor antagonists [228,229]. In addition, a novel modulator of dopamine D2 receptors for the treatment of drug dependence exerts its therapeutic effect by suppressing the interaction between D2L receptors and FABP3 [127]. These novel compounds represent promising candidates for future drug development, and may pave the way for more personalized and precise treatments for dopamine receptor-related disorders.

11. Conclusions

In conclusion, this review article provided an overview of the brain distribution and physiological functions of dopamine D1–D5 receptors, emphasizing their involvement in disorders arising from dysfunction, with a particular focus on representative brain nuclei. Predominantly, by spotlighting the striatum, encompassing the caudate nucleus, putamen, nucleus accumbens, and olfactory tubercle, as well as projection networks including the prefrontal cortex, subthalamic nucleus, amygdala, hippocampus, substantia nigra, and ventral tegmental area, this review discussed nuclei-specific expression patterns of dopamine D1–D5 receptors, their physiological functions, and potential disorders associated with their dysfunction and mutations. The biological functions of dopamine receptors extend beyond motor function, encompassing cognitive memory, motivation, and drug addiction. Understanding the biology of dopamine receptors not only advances the fundamental

knowledge of the central nervous system, but also provides promising clues for therapeutic interventions. With the global aging society, exploring dopamine receptors as potential therapeutic targets has become crucial. Progress in therapeutic development, coupled with a nuanced understanding of these receptors, opens pathways to innovative strategies for treating conditions like Parkinson's disease and schizophrenia, as well as Alzheimer's disease and drug dependency. Continued research unraveling the molecular complexity of dopamine receptors holds promise for the discovery of new therapies, and ultimately contributes to enhancing neurological health in an aging society.

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