

Review

The role of dopaminergic signalling from physiology to neuroprotection in acute and chronic disorders



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ABSTRACT

The dopaminergic system plays a central role in neuromodulation, involving motor control, reward, and cognition, and exerting its effects through five G protein-coupled receptors (DRD1–DRD5) with distinct tissue distributions and signalling mechanisms. While dopaminergic alterations are known to be associated to neuropsychiatric and movement disorders such as schizophrenia, Parkinson's disease, and Huntington's disease, growing evidence highlights a broader role in neurological and neurodegenerative conditions.

This review explores the dopaminergic system's pathophysiological involvement in acute and chronic diseases such as stroke, spinal cord (SCI), traumatic brain (TBI) injury, and amyotrophic lateral sclerosis (ALS). Beyond characterizing its dysfunction, we aim to examine how this disrupted signalling contributes to the neurodegeneration underlying the neurological and neurodegenerative disorders discussed here, along with the associated pathophysiological factors of inflammation and altered plasticity. We further discuss emerging data supporting the potential of dopamine-based interventions not only to modulate disease mechanisms, but also to confer neuroprotection and reduce tissue damage in both acute and progressive neurodegeneration, while also considering sex-related dopamine alterations.

By integrating findings across diverse conditions, we underscore the importance of advancing dopaminergic research beyond classical disease models into novel therapeutic territory.

1. Introduction

Dopamine (DA) is a key endogenous catecholamine neuromodulator that exerts crucial regulatory functions across both the central and peripheral nervous systems (CNS, PNS) (Klein et al., 2019). In the brain, dopaminergic signalling influences an extensive range of physiological processes including motor control, cognition, motivation, mood regulation, memory consolidation, learning, and reward processing. These functions are primarily mediated through four major pathways: nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular tracts (Beaulieu and Gainetdinov, 2011). Additionally, descending dopaminergic projections from the hypothalamic A11 region contribute to

sensorimotor modulation in the spinal cord (Li et al., 2023).

DA also plays essential roles in organs beyond the nervous system, as it participates to the regulation of cardiovascular tone (Neumann et al., 2023), renal function and natriuresis (Qaddumi and Jose, 2021), gastrointestinal motility (Bove et al., 2019), and hormone release (Fitzgerald and Dinan, 2008), thus contributing to systemic homeostasis (Harris and Zhang, 2012). Additionally, DA has been shown to modulate both innate and adaptive immunity, affecting processes such as cytokine release, cell proliferation, chemotaxis, phagocytosis, and antigen presentation (Levite, 2016; Yoshioka et al., 2020; Yan et al., 2015; Channer et al., 2023). These latter effects are often cell-type- and context-specific, leading to contrasting findings.

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Historically, research on DA has focused on its roles in neuropsychiatric and neurodegenerative disorders, especially schizophrenia, Parkinson's disease (PD) and Huntington's disease (HD) (Birtwistle and Baldwin, 1998; Cepeda et al., 2014; Calabresi et al., 2014; Servillo et al., 2024). Recent advances in molecular and imaging approaches have revealed that dopaminergic dysfunction extends beyond mere alterations in receptor expression, encompassing abnormalities in receptor trafficking, intracellular signalling dynamics, and crosstalk with other neuromodulatory systems. (Wong et al., 2023; Kienast and Heinz, 2006). Beyond chronic neurodegeneration, dopaminergic disruption is increasingly recognized as a key factor in acute CNS conditions like stroke, traumatic brain injury (TBI) and spinal cord injury (SCI), as well as in progressive neurological pathologies such as amyotrophic lateral sclerosis (ALS). In these contexts, DA has been implicated in regulating neuronal survival, plasticity (Song and Cramer, 2025; Calderone et al., 2024) and neuroimmune interactions (Channer et al., 2023; Li et al., 2022).

This review aims to provide an updated and integrative perspective on dopaminergic signalling, with a focus on its involvement in acute and chronic neurological disorders. We specifically discuss how a disruption of the DA pathways may contribute to disease pathophysiology and how these mechanisms can be therapeutically harnessed to promote neuroprotection and limit tissue damage.

2. Dopaminergic pathways and their role in physiology and pathological conditions

As anticipated, there are four dopaminergic pathways in the brain accounting for all DA functions: i) the mesolimbic pathway is implicated in processes such as reward and pleasure and originates in the ventral tegmental area (VTA) and projects to the ventral striatum, or nucleus accumbens (Björklund and Dunnett, 2007; Paulus and Schomburg, 2006), ii) the mesocortical pathway also originates from the VTA but instead innervates the prefrontal cortex, participating in cognition and emotion. This pathway together with the mesolimbic pathway has been linked to addiction, depression, and schizophrenia (Björklund and Dunnett, 2007; Paulus and Schomburg, 2006). iii) The nigrostriatal pathway originates from the neuronal somas in the substantia nigra projecting to the dorsal striatum. This pathway plays an important role in movement and locomotion and compelling evidence suggests that the degeneration of these projections underlies classical PD, featuring by tremors, rigidity, and overall extrapyramidal symptoms (Calabresi et al., 2014; Christine and Aminoff, 2004; Ayano, 2016). iv) Lastly, the tuberoinfundibular pathway refers to a group of dopaminergic neurons in the arcuate nucleus of the hypothalamus innervating the median eminence, and it is known to control the secretion of prolactin from the anterior pituitary gland (Ayano, 2016; Ben-Jonathan and Hnasko, 2001).

DA can exert its neuro-modulatory action by binding five different G protein-coupled receptor (GPCR) subtypes, typically with a Gs/olf- or Gi/o-mediated transduction system. Dopaminergic signalling in specific neuronal subtypes is shaped by receptor expression profiles, receptor heteromerization and intracellular signalling coupling, which collectively modulate pharmacodynamics and signal integration.

There are major subclasses of DA GPCRs: D1-like, receptor types 1 (DRD1) and 5 (DRD5), and those referred to as D2-like, receptor types 2 (DRD2), 3 (DRD3), and 4 (DRD4) (Seeman, 2010; Romanelli et al., 2010). Among them, DRD1 and DRD2 are the most numerous DA receptors in the CNS, while DRD3, DRD4, and DRD5 are present at significantly lower levels. D1-like receptors (including D1 and D5 subtypes) are predominantly located at the post-synaptic level, where they typically mediate excitatory effects. These receptors are coupled to Gs proteins and stimulate adenylate cyclase activity, leading to an increase in intracellular cAMP levels and the promotion of excitatory neurotransmission. (Beaulieu and Gainetdinov, 2011) Differently, D2-like receptors (D2, D3, and D4) are expressed both pre-synaptically, where

they function as autoreceptors that negatively regulate dopamine release, and post-synaptically, where they mainly mediate inhibitory effects. Mechanistically, they couple to Gi/o proteins, thereby reducing intracellular cAMP levels and often inducing neuronal hyperpolarization. (Missale et al., 1998). This functional and anatomical distinction highlights how the two receptor families exert complementary yet opposing influences on dopaminergic signalling: on one side, facilitating transmission through D1-like receptors, and on the other, constraining and fine-tuning it through D2-like receptors. (Romanelli et al., 2010; Wang et al., 2002; Martel and McArthur, 2020).

Accumulating evidence suggests that dopaminergic dysfunction contributes to the pathophysiology of diverse neurological disorders, by impairing neuronal survival (Qin et al., 2022), plasticity (Song and Cramer, 2025; Calderone et al., 2024) and inflammation (Channer et al., 2023; Li et al., 2022; Hu et al., 2023; Adamu et al., 2024). Indeed, beyond the established role in neurotransmission - modulating excitatory/inhibitory balance in synaptic plasticity (Song and Cramer, 2025; Calderone et al., 2024) - DA can activate neuroprotective pathways via receptor-dependent mechanisms, that may vary among physiological or pathological conditions (Beaulieu and Gainetdinov, 2011; Missale et al., 1998). These pathways operate on mechanisms that involve the orchestration of neuronal survival (Qin et al., 2022) and the regulation of inflammation (Channer et al., 2023; Li et al., 2022; Hu et al., 2023; Adamu et al., 2024; Xia et al., 2019). Dopaminergic signalling engages intracellular cascades that regulate the expression and release of neurotrophic factors (Lindholm and Saarma, 2022; Bondarenko and Saarma, 2021; Williams and Undieh, 2009), as well as oxidative stress response (Rasool et al., 2024; Yasunari et al., 2000; Bej et al., 2024), and mitochondrial function (Chen et al., 2008; Buoso et al., 2024). Moreover, DA signalling activation of NLRP3 inflammasome complex (Yan et al., 2015; Xia et al., 2019), drives glial cells toward anti-inflammatory and neuroprotective phenotypes (Xia et al., 2019; Palasz et al., 2023), and lastly influences the function of peripheral immune cells impacting systemic inflammatory responses (Feng and Lu, 2021).

Collectively, these mechanisms contribute to enhanced neuronal resilience and survival, positioning dopaminergic signalling as a potentially critical modulator of damage containment and recovery in multiple acute and chronic neurodegenerative pathologies.

2.1. D1-like receptors in brain function

The D1-like receptor family, DRD1 and DRD5, couples to Gs/olf proteins, activates adenylate cyclase, and increases cAMP levels, leading to PKA activation and downstream phosphorylation of targets like CREB and DARPP-32 (Undieh, 2010; Speranza et al., 2021). In the brain, this pathway promotes the expression of neurotrophic factors and prompts synaptic plasticity and long-term potentiation as well as synaptic strengthening. In addition, activation of intracellular ERK/MAPK pathway contributes to neuronal resilience against oxidative stress and excitotoxicity (Undieh, 2010; Jones-Tabah et al., 2022).

DRD1s are predominantly expressed on striatal medium spiny neurons (MSNs), where they play a key role in motor control and reward-related behaviours (Gerfen, 2023; Soares-Cunha et al., 2016) by enhancing neuronal excitability, facilitating movement initiation, and reinforcing positive outcomes (Gerfen, 2023). Additionally, DRD1 is expressed in the prefrontal cortex, where it modulates the excitability of pyramidal neurons, thereby contributing to working memory and executive functions such as attention and decision-making (Williams and Castner, 2006; Floresco, 2013). It is reported that the disruption of DRD1 signalling is associated with several human disorders, including ischemia, PD, schizophrenia and HD (Jones-Tabah et al., 2022; Arcan-geli et al., 2013; Saulle et al., 2002). Indeed, DRD1 activation produces anxiolytic and antidepressant-like effects, while also promoting neural stem cell (NSC) proliferation, long-term survival, and neuronal differentiation by positively modulating the Wnt/ β -catenin signalling pathway in the hippocampus of PD rats (Mishra et al., 2019). DRD1 also

facilitates neuroprotection in rodent ischemia models by reducing excitatory synaptic transmission in striatal neurons, a process mediated through the activation of PKA and adenosine A1 receptors (Zhang et al., 2008).

In contrast DRD5 is less abundant than DRD1, and is expressed in multiple brain regions, including the hippocampus, thalamus, and hypothalamus where it contributes to cognition and emotional regulation (Carr et al., 2017). DRD5 exhibits higher affinity for DA and higher constitutive activity (Demchyshyn et al., 2000). Models with genetic inactivation of DRD5 showed decreased production of the neurotrophic factor BDNF via the TrkB–Akt signalling axis in the prefrontal cortex (Perreault et al., 2013), as well as altered activity of cholinergic interneurons, which led to worsened motor responses to L-DOPA and increased dyskinesia in a Parkinson's disease mouse model (Castello et al., 2020), underscoring the potential of DRD5 as a therapeutic target.

2.2. D2-like receptors in brain function

D2-like receptors (DRD2, DRD3, DRD4) couple to Gi/o protein, inhibit adenylyl cyclase and reduce cAMP levels. They also engage β -arrestin-dependent pathways, modulating Akt/GSK-3, MAPK/ERK, and ion channels (Beaulieu and Gainetdinov, 2011) prompting to reduce oxidative stress, to regulate inflammation and to support neuronal survival (Channer et al., 2023; Cousineau et al., 2020; Tritsch and Sabatini, 2012).

DRD2, the most abundant subtype, has two isoforms: the pre-synaptic short form (DRD2S) and the post-synaptic long form (DRD2L) (Lindgren et al., 2003; Reiner-Link, 2024; Usiello et al., 2000). The presence of isoforms and their region-specific roles highlight the DRD2's complexity and its involvement in diverse CNS functions (Lindgren et al., 2003). DRD2 is highly expressed in MSNs of the dorsal striatum, where it plays a key role in fine-tuning motor control (Gerfen, 2023; Soares-Cunha et al., 2016). In the prefrontal cortex, DRD2 regulates executive function, working memory, and synaptic plasticity by modulating both GABAergic and glutamatergic transmission (Cousineau et al., 2020; Goto et al., 2010; Tseng and O'Donnell, 2007).

In preclinical models, pharmacological modulation of DRD2 appears to facilitate neuroprotective mechanisms. For example, bromocriptine and quinpirole, two DRD2 agonists, prevent glutamate-induced cytotoxicity in rat cortical neurons via the PI3K/Akt signalling cascade, that leads to the upregulation of the anti-apoptotic protein Bcl-2, thereby promoting cell survival (Kihara et al., 2002). This protective effect was diminished when the PI3K inhibitor LY294002 was applied to the culture, confirming the essential role of the DRD2-dependent PI3K/Akt pathway in mediating neuroprotection (Kihara et al., 2002). Similarly, DRD2-dependent activation of the PI3K/Akt pathway promotes cell survival and reduces apoptosis in dopaminergic cell lines, as shown in experimental studies. (Nair et al., 2003). In the context of neurodegenerative disorders, experimental data indicate that DRD2 agonism exerts neuroprotective effects on mitochondrial function, by inhibiting the cAMP/PKA intracellular pathway in a mouse model of familial PD (Tozzi et al., 2018). Also, in an MPTP-induced mouse model of PD, DRD2 activation exerted anti-apoptotic effects by suppressing astrocytic NLRP3 inflammasome assembly through a β -arrestin2-dependent mechanism (Zhu et al., 2020). However, these findings are currently limited to preclinical studies, and their translation to human pathology and therapeutic application has yet to be established.

The DRD3 subtype is predominantly located in limbic regions, including the nucleus accumbens, hippocampus, albeit it is also expressed in the prefrontal cortex, altogether DRD3 modulates emotional and cognitive functions, and its protective role is increasingly recognized in neuropsychiatric and neurodegenerative disorders (Kiss et al., 2021; Pich and Collo, 2015). For example, in models of neuropsychiatric disorders, as schizophrenia and depression, the activation of DRD3 exerts antidepressant effects by inhibiting pro-inflammatory cascades and enhancing neurotrophic signalling (Wei et al., 2021;

Leriche et al., 2004; Wang et al., 2018). In PD, the activation of DRD3 has been described as neuroprotective in mouse models by restoring DA levels in the striatum, reducing dopaminergic neuron loss in the substantia nigra, and improving behavioural outcomes (Lao et al., 2013; Li et al., 2010). While mechanistically compelling, these findings remain preclinical and require validation in translational or clinical settings.

DRD4, predominantly localized in the prefrontal cortex, amygdala, and hippocampus (Defagot et al., 1997; Xiang et al., 2008; Mrzljak et al., 1996), plays interesting roles in attention and decision-making (Oak et al., 2000). Functionally, in sub-chronic phencyclidine (PCP)-treated rats, a model of schizophrenia-like cognitive impairment, DRD4 agonists can modulate network activity, thereby reversing cognitive deficits of rats, thus suggesting a role for DRD4 in preserving cognitive function (Miyauchi et al., 2017). In the same study, DRD4 agonism also enhanced the cognitive benefits of lurasidone—an atypical antipsychotic with low affinity for DRD4—when administered according to an add-on strategy. Surprisingly, the blockage of DRD4 was shown to exert neuroprotective effects in ischemic brain injury models, by reducing oxidative stress-induced apoptosis, thus limiting neuronal damage after stroke (Okada et al., 2005).

Finally, it is important to consider that DRDs can form heterodimers with other G protein-coupled receptors, as demonstrated in several studies (Perreault et al., 2014; Maggio et al., 2009; Missale et al., 2010). The heteromerization of these receptors introduces additional layers of functional diversity and regulatory mechanisms, thereby complicating pharmacological targeting and modulation of the dopaminergic system in different pathological conditions.

2.3. DA signalling in the spinal cord

Beyond its well-established functions in the brain, DA also plays an important modulatory role in the spinal cord. DA is primarily delivered to the spinal cord via descending projections from the hypothalamic A11 region (Hou et al., 2016), although local synthesis occurs under certain conditions, such as in a case of an injury (Hou et al., 2016). For example, after spinal cord injury, some experimental studies reported that local synthesis of DA is present due to the expression of tyrosine hydroxylase (TH), the rate-limiting enzyme for dopamine synthesis (Hou et al., 2016). DRDs, except for DRD2 auto-receptors (Pappas et al., 2008), are expressed in motoneurons and interneurons and such receptors are non-uniformly distributed through dorsal and ventral horns of the spinal cord (Zhu et al., 2007). The activation of DRD2 can promote neuronal survival by reducing oxidative stress, inhibiting apoptotic signalling, and enhancing anti-apoptotic pathways, as well as by suppressing inflammatory responses in experimental models of spinal cord degeneration (Liu et al., 2023; Iwasaki et al., 1997; Tanaka et al., 2011). Interestingly, experimental studies explored the role of DRD1 in models of neuropathic pain focusing on its interaction with DRD2 and the formation of DRD1-DRD2 receptor complexes. It has been demonstrated that inhibiting the DRD1-DRD2 complex by Levo-corydalmine, can relieve the neuropathic pain via a downstream inhibition of PKC γ , CaMKII, MAPK, and CREB signalling pathways and the decrease of excitability of spinal neurons (Bao et al., 2021). DRD3 was also reported in the superficial layer of the dorsal horn at the cervical and lumbar levels in the rat spinal cord (Levant and McCarron, 2001). Regarding DRD4, its modulation has been linked to reduced neuroinflammation and enhanced neuronal survival in experimental models of ALS. Specifically, DRD4 activation has been shown to decrease TNF- α expression in the spinal cord, which correlates with a delayed loss of motor neurons in ALS mice, namely SOD1G93A mice (Tanaka et al., 2008). Regarding DRD5 reports have pointed to a possible action in the development of chronic pain (Megat et al., 2018). Moreover, during development, DA signalling plays a dynamic and stage-dependent role in influencing spinal cord architecture and function (Sharples et al., 2020; Lambert et al., 2012; Reimer et al., 2013). In the zebrafish embryo, descending dopaminergic projections from the brain activate DRD4 in the spinal

cord, modulating spinal progenitor cell fate through neural differentiation (Reimer et al., 2013). During rodent perinatal development, endogenous spinal DA levels are low, exerting an inhibitory effect via D2-like receptors that imposes, a developmental “brake” on premature neuronal excitability. As DA concentration rises, D1-like receptors are engaged, facilitating motoneuron excitability and rhythmic motor output (Sharples et al., 2020).

In summary, dopaminergic pathways exhibit fine-tuning modulation of various physiological processes via different receptors with distinct localization and projecting patterns. Understanding how to modulate dopaminergic pathways through DRDs and their different intracellular signalling cascades is crucial for the development of targeted therapies for neurological disorders.

3. Dopaminergic signalling in acute brain injuries

A large body of evidence from preclinical and clinical studies shows that dopaminergic pathways undergo substantial alterations following acute CNS injuries, including ischemic stroke, traumatic brain injury (TBI), and spinal cord injury (SCI) (Gower and Tiberi, 2018; Lan et al., 2019; Sharples et al., 2014). Following acute CNS insults, disturbances in DA signalling can contribute to activation of secondary injury cascades, potentially exacerbating neuronal damage, inflammation, cognition and impairing recovery (Jiang et al., 2023; Chen et al., 2017; Sami and Faruqi, 2015). Conversely, pharmacological modulation of DRDs or dopamine metabolic pathways has shown promising neuroprotective effects in experimental models, underscoring the multifaceted role of dopamine signalling in the pathophysiology and recovery processes following acute neural injury. Therefore, an in-depth understanding of DA-mediated molecular mechanisms is essential for developing targeted therapeutic interventions aimed at reducing injury severity, mitigating delayed neuronal damage, and enhancing neurological recovery post-injury.

3.1. Dopaminergic alterations in stroke

Stroke represents the third-frequent cause of mortality and leading cause of long-term disability in industrialized countries (Martin et al., 2025). Lesions involving areas with high dopaminergic innervation—such as the basal ganglia (particularly the caudate and putamen), frontal cortex, and midbrain structures account for more than 25 % of all strokes and are more likely to disrupt DA signalling (Tamura et al., 1990). This selective vulnerability is partly explained by the fact that MSNs, which constitute the major output of the striatum, are strongly regulated by dopaminergic inputs and undergo rapid maladaptive changes during hypoxic-ischemic stress (Arcangeli et al., 2013), while inhibition of aberrant Cdk5 activity preserves dopaminergic signalling and improves MSN survival during ischemia (Meyer et al., 2014). These areas are involved in motor control, reward, and executive functions, and disruption here can have broad consequences on various neurological functions ranging from motor control to mood, potentially influencing acute outcomes, long-term recovery (Gower and Tiberi, 2018; Khalilian et al., 2025; Bacigaluppi et al., 2009).

It is also crucial to distinguish between acute and chronic ischemic processes. Most ischemic strokes present acutely due to abrupt vessel occlusion, but other conditions like small vessel disease represent more subtle ischemic processes with cumulative damage (Mu et al., 2024). This process gradually impairs dopaminergic pathways, especially projections from the ventral tegmental area (VTA) and substantia nigra to the frontal cortex and striatum (Trutti et al., 2019). As these pathways deteriorate, the brain's ability to regulate mood, motor functions, and executive functions decline (Trutti et al., 2019). The resulting dopaminergic imbalance manifests clinically as executive dysfunction, depression, and gait disturbances—hallmark features frequently observed in patients with subcortical ischemic vascular disease (Seo and Ryu, 2023; Chui, 2007; Roman et al., 2002; Karalija et al., 2022; Li et al., 2024).

Indeed, 1–4 % of stroke patients develop movement disorders (Suri et al., 2018) or more in general extrapyramidal symptoms, including vascular parkinsonism that accounts for 4.4 %–12 % of all cases of parkinsonism, particularly when lesions affect the basal ganglia or its connections (Udagedara et al., 2019). Furthermore, subcortical ischemic lesions may disrupt corticostriatal and thalamostriatal loops, compounding motor dysfunction through dopaminergic-independent mechanisms (Mori, 2002), but that may result in significant interaction with DA tone.

Upon ischemic injury DA levels rapidly increase in the striatum during the early phase and a correlation injury size and DA release has been found (Ahn et al., 1991). Some studies have shown that depletion of dopaminergic projections to the striatum prior to an ischemic insult can confer neuroprotection (Globus et al., 1987; Ren et al., 1997). This potential neuroprotective effect, attributed to the reduction of DA-mediated excitotoxicity during ischemia still requires confirmation. Indeed, other studies have demonstrated that the administration of exogenous dopamine precursors can significantly reduce infarct size and improve neurological outcomes in preclinical models of stroke, primarily through the modulation of pro-inflammatory cytokine release and the attenuation of oxidative stress (Ruscher et al., 2012; Wang et al., 2022) (Scheidtmann et al., 2001; Lokk et al., 2011). Moreover, neurostimulatory drugs such as amantadine, that increase DA levels, improved cognitive and functional recovery after a stroke, when administered to patients during acute stroke phases (Gagnon et al., 2020). In sum, although some results remain conflicting, the evidence for fluctuating dopamine levels after stroke provides a strong rationale for targeting the dopaminergic system with time- and dose-tailored interventions to mitigate neuronal injury and limit cognitive decline.

3.2. Dopaminergic alterations in trauma

TBI is a leading cause of death and disability following significant head injuries (Park et al., 2008), with more than 50 million TBIs occurring worldwide each year (Feigin et al., 2013). Brain injury fatality rates vary substantially across regions, and the condition imposes a considerable economic burden globally (Li et al., 2016). Like ischemic stroke, traumatic brain injury (TBI) is classified based on lesion location (e.g., frontal cortex, basal ganglia, midbrain), severity (ranging from mild to severe), and injury type (focal vs. diffuse). TBI can arise from a single acute event or from repeated mild injuries - such as those sustained in contact sports or specific occupational settings - which may cumulatively disrupt dopaminergic circuits and contribute to the risk of long-term neurodegenerative processes (Hawryluk and Manley, 2015). Repeated concussions may lead to progressive dopaminergic dysfunction, contributing to cognitive decline and parkinsonism over time. Indeed, DA influences key mechanisms underlying TBI including, oxidative stress, mitochondrial function, reward/motivation systems, and neuroplasticity, positioning it as a central modulator of both injury and recovery phases (Mata-Bermudez et al., 2024).

Evidence suggests that dysregulation of dopaminergic signalling following acute insults, such as TBI, can exert both deleterious and potentially reparative effects, depending on complex factors including the timing of DA fluctuations, the receptor subtypes involved, and the specific signalling pathways activated. Indeed, animal and clinical studies have characterized DA dysfunction following TBI and despite the difficulties of its diffuse nature and variable presentation, a series of temporally specific alterations in DA neurotransmission have been identified (Lan et al., 2019; McIntosh et al., 1994). Following TBI, dopaminergic signalling changes exhibit a biphasic pattern: an acute hyperactive phase, characterized by elevated DA levels and increased DRD1 activity, followed by a hypofunctional phase marked by reduced DA overflow and alterations in dopaminergic metabolism (both DAT and TH expression). At later stages, neuronal loss and receptor down-regulation produce a decrease in DA levels as observed in experimental models of trauma (Lan et al., 2019; McIntosh et al., 1994). As in ischemic

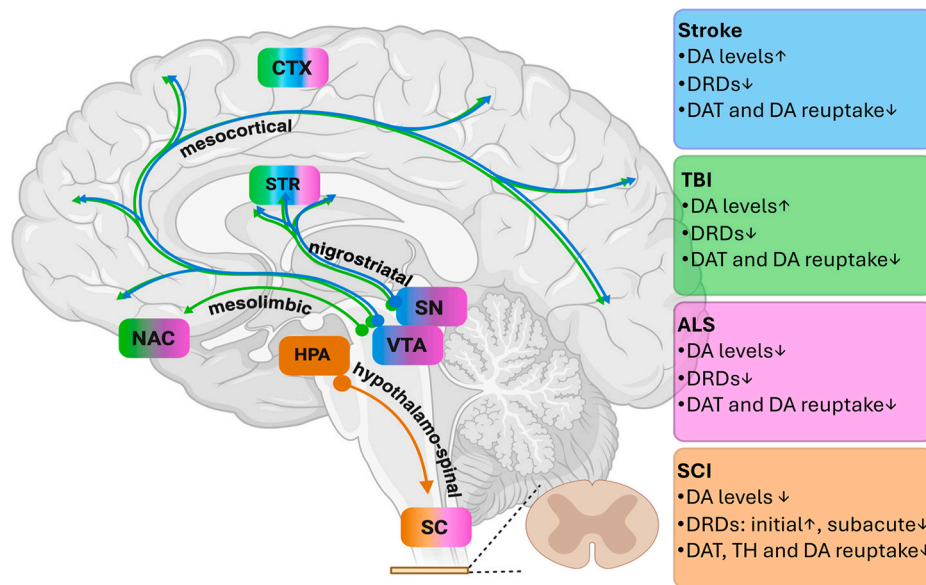


Fig. 1. Schematic representation of the human brain and spinal cord illustrating the dopaminergic system in acute and chronic neurological diseases. The figure highlights the main dopaminergic pathways in the CNS: the nigrostriatal pathway (from the substantia nigra pars compacta [SN] to the dorsal striatum [STR]); the mesocortical pathway (from the ventral tegmental area [VTA] to the cortex [CTX]); and the mesolimbic pathway (from the VTA to the nucleus accumbens [NAC]). In the lower right, the hypothalamo-spinal pathway connects the hypothalamic nuclei (HPA) to the spinal cord (SC). The colour code indicates the involvement of each dopaminergic pathway in the neurological conditions listed in the boxes, including stroke, traumatic brain injury (TBI), spinal cord injury (SCI), and amyotrophic lateral sclerosis (ALS). Each box summarizes the specific dopaminergic alterations associated with the respective condition. **Abbreviations:** DA, dopamine; DRDs, dopamine receptors; TH, tyrosine hydroxylase; DAT, dopamine transporter. Image created with [BioRender.com](https://www.biorender.com).

stroke, DA exerts heterogeneous effects after TBI, depending on factors such as timing of treatment and the specific receptor subtypes engaged, as shown in experimental studies. In the early phase after injury, acute, massive dopamine release can lead to excitotoxic damage through a dysregulated interplay with the glutamatergic system, as well as by fostering oxidative stress via reactive oxygen species, ultimately contributing to neuronal loss (Vaarmann et al., 2013). On the other hand, dopamine has also been shown to act as an intrinsic modulator of neuroinflammation and neuronal apoptosis by regulating receptor-interacting protein kinase 1 (RIPK1) signalling. In particular, activation of DRD1 appears as a promising therapeutic target in TBI (Luo et al., 2024). Moreover, acute, subacute and chronic pharmacological blockade of DAT with methylphenidate (MPH) at different stages after TBI, have shown benefits including restoration of DA synthesis and/or its release from dopaminergic terminals (Kline et al., 1994; Kline et al., 2000; Wagner et al., 2009). Altogether, these findings emphasize that dopaminergic signalling plays a dual and temporally dynamic role after traumatic brain injury, acting as both a mediator of early neurotoxic cascades and a potential target for neurorestorative interventions, thereby representing a promising yet complex avenue for therapeutic modulation.

3.3. Dopaminergic alterations in spinal cord injury

Spinal cord injury (SCI) is generally heterogeneous and therefore divided into traumatic and non-traumatic aetiologies, suggesting important epidemiological distinctions, thus its incidence varies worldwide. It is defined as damage to the spinal cord that temporarily or permanently causes changes in its function and can be caused by a mild or severe physical impact, or by non-traumatic aetiologies (tumour, infection or degenerative disc disease) (Ahuja et al., 2017). Moreover, both the acute phase following SCI (e.g., compression, contusion) and the following chronic phases (inflammation, gliosis, maladaptive plasticity) may lead to the dopaminergic disruption. Following a SCI, levels of DA and its receptors abundance decrease in the spinal cord particularly below the site of injury, due to the disruption of descending fibres

projecting from the dopaminergic A10 and A11 nuclei of the posterior hypothalamus, (Sharples et al., 2014). Animal models have shown that the disruption of these pathways leads to reduced dopaminergic modulation of spinal circuits with consequent impairment of locomotion and recovery (Sharples et al., 2014). As described for ischemic stroke and TBI, a multifaceted role of DA in SCI can influence neuronal loss and neuroinflammation (Sharples et al., 2014; Jiang et al., 2023). The early loss of DA levels after SCI suggests that DA may be beneficial after SCI. In line with this, emerging studies have shown the potential benefit of DA in attenuating the secondary damage following SCI by inhibition of the NLRP3 inflammasome activation and pyroptosis, thus reducing neuronal loss and improving locomotion recovery (Jiang et al., 2023). In another study, NLRP3 inflammasome activation was successfully inhibited by administering a DRD1 agonist (A-68930) in a rat model of SCI leading to reduced levels of inflammatory cytokines, attenuation of the histopathology and enhanced locomotion recovery (Jiang et al., 2016).

A comprehensive understanding of the changes of dopamine signaling in neurological diseases is crucial for the development of targeted therapeutic strategies (Fig. 1).

3.4. Sex specific expression of DRD

DRD expression and anatomical distribution differ between biological sexes under physiological conditions, as well as across several disorders—particularly those involving behavioural responses. (Hasbi et al., 2020). Studies on the incidence, natural history, and prognosis of several pathological conditions involving activation of DA pathways clearly indicated that sex is a major determinant of the global burden of neurological diseases (Collaborators, 2024). Nevertheless, literature investigating sex-specific effects of DRD in many of the conditions discussed in this review remains limited and lacks robust findings. Experimental studies so far rarely report results stratified by sex with some exceptions – for instance, in TBI (Wagner et al., 2007), where a significant reduction in hippocampal DRD2 expression was observed in male, mice, with females remaining largely unaffected. Moreover, as above

Table 1
Sex-differential DRD expression or related outcomes.

Disease	DRD expression path and effect by biological sex		Interpretation
	female vs. male effects		
TBI	Females: Lower baseline D2; D2 expression little affected by TBI	Males: Higher baseline D2; ↓ after TBI (notably in dentate gyrus)	Altered reward behaviour (Iannucci et al., 2023)
TBI	Amantadine vs. placebo (TBI clinical trial); about 25 % female participants received amantadine.		Recovery faster in the amantadine group no sex related difference analysed (Giacino et al., 2012)
Stroke	Systematic review of amantadine (n = 121) and modafinil (n = 120) use in post-stroke patients.		No sex-stratified data reported, no consistent improvement in motor or cognitive performance outcomes. (Gagnon et al., 2020)
ALS	Phase 1/2a clinical trial in ALS with ropinirole in 20 participants		No data shown on sex related differences (Morimoto et al., 2023)

Table 2
Neuroprotection in targeting dopaminergic signalling.

Mechanism	Acute Phase (Neuroprotection or damage)	Post-Acute Phase (Plasticity & Recovery)
Dopamine Receptor-mediated activation	Reduction of excitotoxicity, stabilization of ionic homeostasis (Jones-Tabah et al., 2022; Vaarmann et al., 2013; Bozzi et al., 2000; Bales et al., 2010); evidence of neurotoxicity (Saulle et al., 2002)	Modulation of dopamine receptor activity supports network rebalancing and circuit repair (Luo et al., 2024).
Antioxidant & anti-inflammatory effects	Suppression of oxidative stress and limitation of microglial overactivation, astocytosis (Ruscher et al., 2012; Bales et al., 2010)	Maintenance of a supportive inflammatory milieu for tissue remodelling (Jiang et al., 2023; Jiang et al., 2016; Bales et al., 2010)
Neuroplasticity & recovery	Indirect preservation of neurons and synapses by preventing damage (Klein et al., 2019).	Enhancement of synaptogenesis, dendritic growth, and reorganization (Song and Cramer, 2025; Scheidtmann et al., 2001).

reported, studies investigating post-stroke treatments, failed to demonstrate significant effects of mir363-3p administration immediately after stroke, whilst another study reported a positive impact, particularly on depressive behaviour, in female rats. Unfortunately, there is currently a lack of studies investigating sex specific effects of DRD treatments in stroke or in motor neuron diseases. As previously mentioned, two studies exploring the effect of DA agonists on post stroke rehabilitation included a small sample size with limited representation of women and results were not stratified by sex (Scheidtmann et al., 2001; Lokk et al., 2011). Similarly, another multicentric study exploring the effects of amantadine vs. placebo on the neuropsychiatric inventory score (NPI) after TBI, included a small proportion of women (25,6 % placebo vs. 20 % amantadine) with lack of sex specific stratified results (Hammond et al., 2015). Indeed, future studies should stratify results by sex and investigate sex-related differences, both in the effects of dopamine-targeted treatments and in the underlying signalling alterations observed in neurological diseases (Table 1).

4. Therapeutic approaches targeting DA in acute injuries

Both preclinical and clinical studies have identified dopaminergic

pathways as possible therapeutic targets to improve locomotion impairments after SCI (Sharples et al., 2014) or neuronal damage and cognitive deficits in ischemia and trauma (Lan et al., 2019; Ruscher et al., 2012). Among the available approaches that have been tested to target dopaminergic signalling, which often require intracerebral or intrathecal delivery of DA, the development of candidate drugs capable of crossing the blood-brain barrier (BBB) has been prioritized in most studies. (Sharples et al., 2014). Owing to its neuroprotective potential, DRD2 has been extensively targeted across various disease models. Indeed, a wide range of pharmacological agents targeting this receptor are already in clinical use, primarily for the long-term management of conditions such as PD and schizophrenia (Horowski and Löschnann, 2019; Zhu et al., 2017). More recently, there has been increasing interest in repurposing some of these drugs for the treatment of acute brain injuries, including ischemic stroke, TBI and SCI (Table 2). Indeed, when evaluating its efficacy, it should be considered that the effects of DRD manipulation may be more complex than initially anticipated and could even have detrimental consequences, as suggested by studies indicating context-dependent efficacy (Saulle et al., 2002).

These agents may exert neuroprotection by modulating neuro-inflammation, reducing oxidative stress and by directly promoting neuronal survival pathways with promising implications in the clinical outcomes such as the reduction of the infarct size and tissue damage, as well as the improvement of cognitive performance (Fig. 2).

4.1. DA receptor agonists in acute CNS injuries

Recent preclinical studies in rodent models of ischemia have demonstrated the efficacy of DRD2 agonists in reducing the infarct volume and improving the cognitive outcomes post-stroke (Kaushik et al., 2020). For example, in ischemia, acute administration of bromocriptine in an experimental stroke model has demonstrated neuroprotective effects, reducing ischemia-induced free radical production and preserving neurons in the hippocampal CA1 region (Liu et al., 1995). DRD2 agonists have been administrated also in preclinical TBI studies, mostly within a day of TBI and continued chronically with promising results for the treatment of TBI both acutely and into the long-term. In a rat model of TBI, bromocriptine has shown potent antioxidant properties (Yoshikawa et al., 1994), producing beneficial effects on cognition and survival on CA3 hippocampal neurons (Kline et al., 2004).

Other DRD2 agonists have also shown significant antioxidant and neuroprotective properties. For instance, pramipexole significantly promoted neurological recovery in a rat model of ischemia-reperfusion injury by modulating mitochondrial pathways. When administered immediately after stroke, this DRD2 agonist reduced mitochondrial reactive oxygen species (ROS) and intracellular Ca²⁺ levels, while enhancing mitochondrial membrane potential and oxidative phosphorylation, thereby supporting neuronal survival and functional recovery (Andrabi et al., 2019). Sumanrole, a highly selective DRD2 agonist, has also shown beneficial effects in experimental models of ischemic stroke. In rats, treatment with Sumanrole promoted behavioural recovery and markedly reduced infarct size, likely through modulation of mitochondrial pathways that enhance cellular energy homeostasis and attenuate oxidative damage. (Kaushik et al., 2020). The protective action of DRD2 agonists against oxidative stress-induced damage represents a promising pharmacological strategy for paediatric brain disorders such as neonatal asphyxia, paediatric cardiac arrest with global ischemia, and traumatic brain injury, where oxidative stress, mitochondrial dysfunction, and impaired energy metabolism contribute to neuronal death and lifelong neurological impairment. Identifying effective candidate drugs for these conditions is of utmost urgency, as therapeutic hypothermia, applied immediately after injury, remains the only clinically validated neuroprotective intervention to date (Robertson et al., 2009).

Among DRD agonists, amantadine has been extensively investigated in both preclinical and clinical models of traumatic brain injury (TBI), showing promising results in supporting cognitive recovery

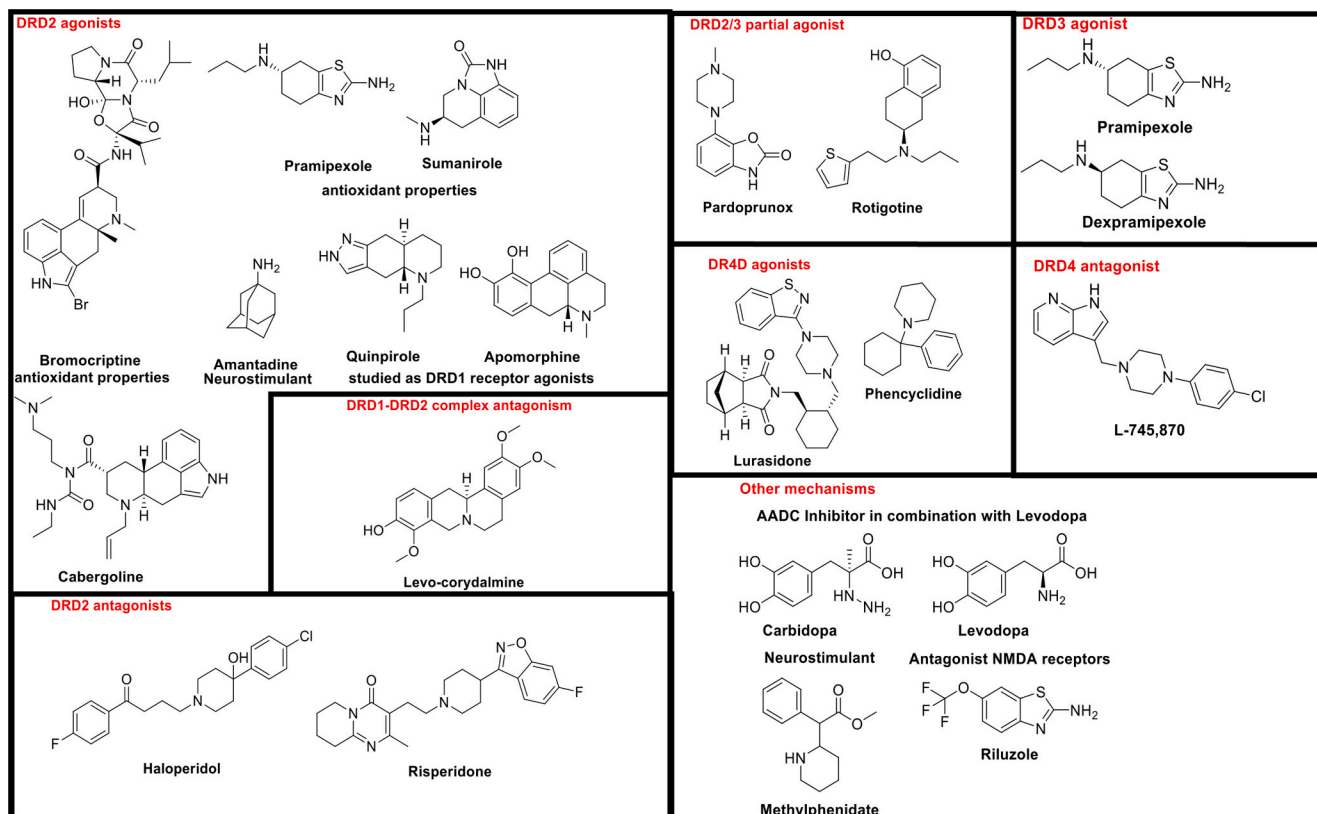


Fig. 2. Drug chemical structures and receptor selectivity.

(Stelmaschuk et al., 2015) and promoting neuroprotection—partly due to its additional anti-glutamatergic properties. Excessive glutamatergic transmission following brain injury leads to excitotoxicity, characterized by excessive calcium influx, mitochondrial dysfunction, and neuronal death. However, this complex multimodal mechanism of action can complicate experimental interpretation, and although amantadine remains a promising therapeutic option, its pleiotropic effects warrant careful mechanistic investigation (Stelmaschuk et al., 2015; Spritzer et al., 2015) (Hammond et al., 2015; Osier and Dixon, 2016).

Quinpirole administration following traumatic brain injury (TBI) has been shown to attenuate neuroinflammatory responses through modulation of the DRD2/Akt/GSK3- β -signalling pathway, thereby exerting neuroprotective effects. These findings suggest that DRD2 activation by quinpirole may offer a safe and effective therapeutic strategy to counteract TBI-induced neurodegeneration (Alam et al., 2021). In peripheral models, quinpirole has been administered to rats with chronic allodynia to evaluate the effects of DRD2 agonists in neuropathic pain treatment. These experiments provided preliminary evidence supporting the potential use of DRD2 agonists, such as quinpirole, for neuropathic pain relief (Cobacho et al., 2014). DRD agonists, such as quinpirole (a selective DRD2/DRD3 agonist) and apomorphine (a mixed DRD1/DRD2 agonist), have been investigated in experimental models to assess their neuroprotective efficacy, though DRD1-specific compounds have been less extensively studied than DRD2 agonists. Interestingly, in a rat model involving intrastriatal malonate injection, which induces lesions resembling focal ischemic injury, increasing concentrations of DRD1-, DRD2-, or mixed DRD1/DRD2-agonists exhibited distinct dose-dependent neuroprotective profiles against malonate-induced toxicity (Armentero, 2002).

4.2. DA receptor antagonists in acute CNS injuries

Interestingly, DRD antagonists may have also beneficial roles in

acute brain injuries, albeit their role in modulating neurological outcomes is less clear and still debated. Beneficial effects have been described in neurological conditions including models of brain lesion, ischemia, and excitotoxicity. For example, in the same model of malonate-mediated striatal lesion mentioned above, a significant reduction of the lesion was observed when a DRD2 antagonist was administered (Armentero, 2002). In a gerbil model of brain ischemia, systemic administration of DRD4 antagonist provided beneficial effects by attenuating ischemia-induced damage of hippocampal CA1 neurons (Okada et al., 2005). In an experimental model of mild TBI, where haloperidol, a dopaminergic antagonist, but not apomorphine (agonist) significantly ameliorated the task performance in behavioural tests, indicating a DRD2 mediated recovery of post traumatic memory deficits. However, the same study has confirmed in a dose-dependent experiment, that also a combined treatment with DRD1 and DRD2 antagonists, exerted a significant additive effect in improving these deficits, due to the mutual interaction between DRD1 and DRD2 in mediating a response (Tang et al., 1997).

Despite these positive reports, overall DA receptor antagonists such as haloperidol and risperidone are commonly used in TBI, mostly for their sedative properties, rather than for psychosis and agitation that are common outcomes of trauma, but not for neuroprotection (Stanislav, 1997). Indeed, antagonizing the dopaminergic system is known to cause parkinsonian-like symptoms and delayed motor recovery.

While direct agonism or antagonism of DA receptors has shown significant potential in modulating outcomes of acute brain injury, therapeutic strategies are not limited to receptor targeting alone. Indirect modulation of the dopaminergic system—through influencing DA synthesis, metabolism, or reuptake—offers additional avenues for intervention (Bales et al., 2010). Agents that enhance DA availability or prevent its degradation, such as monoamine oxidase inhibitors (MAOIs) or DA reuptake blockers (MPD, methylphenidate), may amplify beneficial dopaminergic signalling without the risks associated with receptor

overactivation (Kline et al., 2000; Sivenius et al., 2001). Conversely, reducing DA synthesis or accelerating its breakdown could be advantageous in contexts where excessive dopaminergic activity contributes to neurotoxicity. These indirect approaches provide a broader and more nuanced therapeutic landscape for leveraging the neuroprotective and regulatory roles of DA in acute CNS injuries (Osier and Dixon, 2016).

5. Harnessing dopaminergic signalling for neuroprotection in chronic motor neurodegeneration

Amyotrophic lateral sclerosis (ALS) is a fatal sporadic or genetic neurodegenerative disorder characterized by the progressive degeneration of upper and/or lower motor neurons, leading to a gradual decline in motor function (Riva et al., 2024; Bono et al., 2025) (Van Es, 2024). The dopaminergic system appears to be subtly but significantly involved in ALS pathology. ALS seems in fact to involve a more widespread dopaminergic dysfunction, extending to the limbic system and underscoring the multisystemic nature of the disease (Mavridis and Pyrgelis, 2023; Brunet et al., 2020). As early as the late 1990s, decreased DA levels in the caudate-putamen and nucleus accumbens, along with loss of dopaminergic neurons in the VTA and substantia nigra pars compacta, were reported in the ALS mice of (SOD1G93A) (Kostic et al., 1997). Imaging studies in the same mouse model confirmed VTA damage, with up to 50 % loss of dopaminergic neurons and vacuolization of the remaining cells at disease end-stage (Jouroukhin et al., 2013).

In humans, dopaminergic involvement in ALS has also been documented (Brunet et al., 2020; Takahashi et al., 1993; Kato et al., 1993). Increased DA levels and reduced levels of its metabolite DOPAC were found in serum and cerebrospinal fluid (CSF) (Janssens et al., 2020), moreover decreased DAT immunoreactivity was described in PBMC of ALS patients (Buttarelli et al., 2006). PET imaging with [¹⁸F]-fallypride revealed a reduction in DRD2/DRD3 availability in the nucleus accumbens and other subcortical regions (Mavridis and Pyrgelis, 2023; Takahashi et al., 1993; Fu et al., 2017).

Post-mortem studies have shown neuronal loss and TDP-43, namely the gene product of TARDBP, deposits in the nucleus accumbens (Mavridis and Pyrgelis, 2023; Brettschneider et al., 2013). SPECT imaging in a subset of sporadic ALS patients also indicates modest dopaminergic deficits, including reduced striatal DA transporter (DAT) binding of IPT (N-(3-iodopropen-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl)-tropane), a cocaine analogue that selectively binds to the DAT located on dopaminergic nerve terminals (Borasio et al., 1998).

5.1. DA receptor agonists and antagonists in ALS

Although direct evidence of spinal dopaminergic dysfunction in ALS patients or animal models is lacking, several studies suggest that DA signalling influences ALS pathology. For example, dopaminergic modulation has been shown to be beneficial in the SOD1H46R ALS mouse model. Treatment with the DRD2 agonist bromocriptine exerted protective effects via anti-inflammatory and antioxidant mechanisms, reducing glial activation, upregulating antioxidant genes such as ATF3 and HO-1 and preserving spinal motor neurons (Tanaka et al., 2011). Pharmacological modulation of DRD4 with the antagonist L-745,870 in the same murine model can influence neuroinflammatory responses and neuronal survival in the spinal cord resulting in suppressed microglial activation, reduced expression of TNF- α in the spinal cord other than a delayed loss of motor neurons (Tanaka et al., 2008). However, interactions between the dopaminergic system and other neuromodulatory pathways may complicate therapeutic outcomes. In TDP-43 ALS mouse models, DRD2 activation was shown to counteract the neuroprotective effects of adenosine A2A receptor signalling by suppressing the cAMP/PKA pathway, ultimately exacerbating disease progression (Lai et al., 2018).

Despite these context-dependent effects observed in murine models, an iPSC-derived motor neuron-based screening pointed to a significant

role for DA signalling in ALS pathophysiology and have prompted interest in dopaminergic therapies. A phenotypic screen using SOD1A4V iPSC-derived spinal motor neurons identified DRD2 as a modulator of neuronal hyperexcitability; DRD2/3 agonist bromocriptine and the selective DRD2 agonist Sumanitrolol enhanced motor neuron survival, supporting a pro-survival role of DRD2 signalling in ALS (Huang et al., 2021).

DA agonists traditionally used in Parkinson's disease have been repurposed in preclinical ALS studies with promising results showing neuroprotective properties in preclinical ALS models, potentially via DA-dependent mechanisms or alternative pathways such as reducing oxidative stress and preserving mitochondrial function. Bromocriptine, in addition to its efficacy in animal models (Huang et al., 2021), was tested in a Phase 2a randomized, placebo-controlled trial on ALS patients. When administered as an add-on to riluzole, it was well tolerated by patients and led to improvements in motor function and quality of life, particularly in communication and swallowing (Nagata et al., 2016).

Among DRD2 agonists, ropinirole was identified through iPSC-based phenotypic screening as effective in ameliorating pathological features in ALS motor neurons with FUS and TDP-43 mutations, including mitochondrial damage and oxidative stress. However, its effects in iPSC-derived SOD1 mutant motor neurons were limited to partial mitochondrial improvement, suggesting mechanistic differences across different ALS subtypes (Fujimori et al., 2018). A subsequent Phase 1/2a trial (ROPALS) confirmed the safety of the drug and suggested a possible delay in disease progression (Morimoto et al., 2023). Pramipexole, a DRD3-preferring agonist, has been shown to exert neuroprotective effects by maintaining mitochondrial function and reducing oxidative stress (Okano et al., 2020; Okano and Morimoto, 2022). Its R(+) enantiomer, dextramipexole, exhibits minimal dopaminergic receptor activity compared with the S(-) form. Its mechanism of action in ALS is thought to be primarily dopamine-independent, aiming instead to stabilize mitochondrial function, enhance cellular energy metabolism, and reduce oxidative stress, thereby mitigating motor neuron vulnerability. Dextramipexole showed promise in early-phase trials but ultimately failed to demonstrate efficacy in a Phase 3 trial (Alavian et al., 2012) (Wang et al., 2008; Cheah and Kiernan, 2010; Corcia and Gordon, 2012; Cudkowicz et al., 2013; Cudkowicz et al., 2011). Altogether, these findings indicate that dopaminergic dysfunction contributes to ALS pathogenesis and targeting DA-related pathways may offer a promising therapeutic avenue.

6. Recent clinical application of DRD2 agonists

Although direct evidence clarifying role of DRD2 modulators in pathological conditions resembling neurodegeneration remains limited, the aforementioned preclinical studies have undoubtedly paved the way for the development of new therapeutic approaches targeting these receptors.

Several clinical studies have investigated the use of DRD2 modulators in the treatment of psychiatric disorders- for example, more than 700 clinical trials have been conducted in patients with schizophrenia. Fewer trials have been conducted in neurodegenerative disorders, although more than 300 therapeutic trials with DRD2 modulators have been conducted in patients with PD. Despite relatively few studies addressing the potential of DRD2 modulators in other neurodegenerative conditions few clinical investigations have been conducted in ALS. As previously reported in the ROPALS clinical trial (Morimoto et al., 2023), 20 patients with sporadic ALS received ropinirole for 24 weeks in a double-blind phase to evaluate its safety, tolerability, and therapeutic effects. Although the treatment proved to be safe, no significant difference in ALSFRS-R decline was observed during the double-blind phase. Nevertheless, an open-label extension of the study revealed a slower functional decline and prolonged progression-free survival in the ropinirole group. Further validation is needed due to the small sample size.

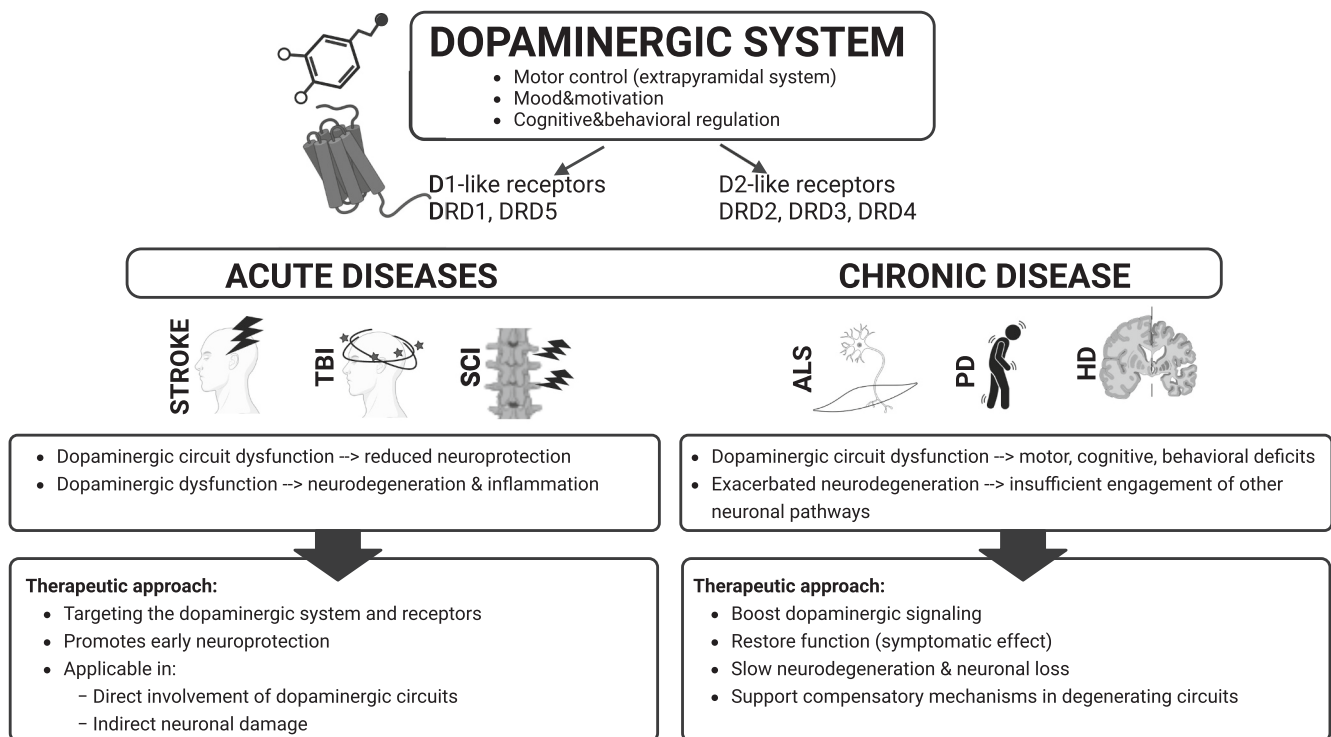


Fig. 3. Schematic overview of the dopaminergic system and its role in acute and chronic neurological diseases. The dopaminergic system regulates motor control, mood, motivation, and cognitive/behavioural functions through **D1-like (DRD1, DRD5)** and **D2-like (DRD2, DRD3, DRD4)** receptors. In **acute neurological diseases** (stroke, traumatic brain injury [TBI], spinal cord injury [SCI]), dysfunction of dopaminergic circuits leads to reduced neuroprotection, neurodegeneration, and inflammation. Therapeutic strategies aim at targeting dopaminergic receptors to promote early neuroprotection, both in conditions with direct dopaminergic involvement and in those with secondary neuronal damage. In **chronic neurodegenerative diseases** (amyotrophic lateral sclerosis [ALS], Parkinson's disease [PD], Huntington's disease [HD]), dopaminergic dysfunction results in motor, cognitive, and behavioural deficits and accelerates neurodegeneration. Therapeutic strategies include boosting dopaminergic signalling to restore function, slowing neuronal loss, and supporting compensatory mechanisms in degenerating circuits. Image created with BioRender.com.

A phase 2a randomized, double-blind, placebo-controlled clinical trial explored the effects of bromocriptine mesylate (a DRD2) in 36 ALS patients (Nagata et al., 2016). Results indicated mild efficacy in some functional and quality-of-life scores, without differences in adverse events between groups. However, a confirmatory trial on larger patient cohorts is needed. Current research on DRD2 agonists and antagonists in TBI, brain ischemia, and SCI remains largely confined to preclinical studies; however the discovery and validation of new ligands in pre-clinical models provides strong rationale for the design of future clinical trials.

Along the same lines, several clinical studies have investigated ropinirole in combination with physiotherapy in patients with moderate motor deficits following stroke. The results indicated that ropinirole was well tolerated, although it did not significantly improve gait velocity compared with placebo (Cramer et al., 2009).

Bromocriptine combined with speech therapy was also tested in non-fluent aphasic stroke patients. Although this was a small clinical trial, results are encouraging, as a significant improvement was observed in several language tests (verbal latency, repetition, reading comprehension, dictation, and qualitative assessments of free speech) (Bragoni et al., 2000).

Similarly to clinical trials in brain ischemia, only a few therapeutic attempts have been conducted in patients with persistent cognitive deficits following TBI. In a clinical trial involving a small cohort of patients with mild brain injury, bromocriptine failed to improve working memory (McAllister et al., 2011). Bromocriptine was also tested in a small cohort of patients with TBI, where treatment led to improved physical and cognitive performance after four weeks of therapy (Martin-Morelle et al., 2016).

Therefore, as in stroke, results in TBI are limited and inconsistent,

with bromocriptine remaining the main DRD2-targeting agent studied.

To provide a more comprehensive overview of DRD2 modulation, we also highlight clinical trials in PD. In 2006, a trial evaluated the efficacy of pramipexole, a DRD2 agonist, administered twice daily compared with placebo (NCT00402233).

Pramipexole has also been tested in more recent PD trials, often as part of ongoing standard therapy for participants receiving additional experimental treatments. For instance, a multicentre, parallel-group, placebo- and pramipexole-controlled study evaluated the efficacy of pargolprunox, a DRD2/3 partial agonist (NCT00335166).

Apomorphine, a potent DRD2 agonist, is currently being evaluated in a phase II multicentre clinical trial involving patients with advanced PD who exhibit motor fluctuations that remain suboptimally controlled with levodopa or levodopa/carbidopa therapy. (NCT02339064).

Cabergoline, another DRD2 agonist, was tested in 2005 in comparison with carbidopa/levodopa therapy for treating nighttime symptoms in PD (NCT00174239).

A more recent clinical trial (NCT06080399) is recruiting PD patients to assess the effects of continuous subcutaneous apomorphine infusion, while rotigotine (a DRD2/3 agonist) was tested in a multicentre, open, randomized trial in idiopathic PD that began in 2021 (NCT06247410).

In general, several DRD2 agonists, including pramipexole, ropinirole, and rotigotine, have consistently demonstrated favourable efficacy outcomes in PD, improving bradykinesia, rigidity, and tremor both as monotherapy in early stages and as adjunct therapy to levodopa in advanced disease.

However, long-term use of these modulators may result in adverse effects, including impulse control disorders, hallucinations, and somnolence. Consequently, further research is required to optimize therapeutic efficacy while accounting for individual risk profiles.

7. Conclusion

Dopaminergic signalling plays a complex and context-dependent role in both acute and chronic neurological conditions, with shared underlying mechanisms such as inflammation, oxidative stress, and excitotoxicity contributing to neuronal injury. In acute pathologies like ischemic stroke, the sudden disruption in blood flow initiates a cascade of inflammatory and oxidative processes, where DA can exacerbate damage through excessive release and auto-oxidation, promoting neurotoxicity. Conversely, in chronic neurodegenerative diseases such as PD or ALS, dopaminergic signalling may exert neuroprotective effects by modulating synaptic plasticity and supporting neuronal survival pathways. These dual roles underscore the importance of contextualizing dopamine's function: while its dysregulation can be detrimental in acute settings, targeted enhancement of specific dopaminergic pathways in progressive conditions may offer therapeutic benefits. Understanding these divergent mechanisms is crucial for the development of effective and targeted neuroprotective strategies across disease types (Fig. 3).

CRedit authorship contribution statement

Martina Di Nunzio: Writing – original draft, Validation, Conceptualization. **Maria Lidia Mignogna:** Writing – review & editing, Validation, Conceptualization. **Marco Bacigaluppi:** Writing – original draft, Validation, Supervision, Conceptualization. **Paola Panina-Bordignon:** Writing – review & editing, Validation, Conceptualization. **Paolo Ragonesi:** Writing – original draft, Validation. **Luca Muzio:** Writing – original draft, Validation, Conceptualization. **Vincenzo Summa:** Writing – original draft, Validation. **Gianvito Martino:** Writing – review & editing, Validation, Resources.

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Declaration of competing interest

The authors declared no conflict of interest.

Data availability

All data generated or analysed during this study are included in this published article.

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