

## Review Article

# The potential roles of dopamine in traumatic brain injury: a preclinical and clinical update

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**Abstract:** Traumatic brain injury (TBI) is one of the leading causes of death and disability, particularly among the young and the elderly. Several therapeutic options have been investigated, including drug interventions or combinational therapies. Although many drugs have shown promising results in the preclinical stage, all have failed in large clinical trials. Targeting the dopamine system is a novel TBI approach that provides benefits to functional outcomes. TBI could damage the dopaminergic system. Alterations in dopamine levels can impact cellular dysfunction and central nervous system (CNS) inflammation. Experimental evidence suggests that dopamine should be considered a first-line treatment to protect cerebral autoregulation and promote cerebral outcomes in TBI. Furthermore, investigation of dopamine-related genetic factors in relation to injury severity could also be of great significance for promoting TBI treatment. Importantly, various clinical lines of evidence have indicated that many dopamine agonists are beneficial when administered following injury in TBI patients. However, side effects of dopamine treatment prevent their use in TBI treatment, and there is a need for ongoing large, prospective, double-blind randomized controlled trials (RCTs) with these medications by the use of standardized criteria and outcomes to fully understand their effectiveness in this patient group. Here, we review the roles of dopamine in TBI and discuss the role that dopaminergic therapies have in neuroprotective strategies.

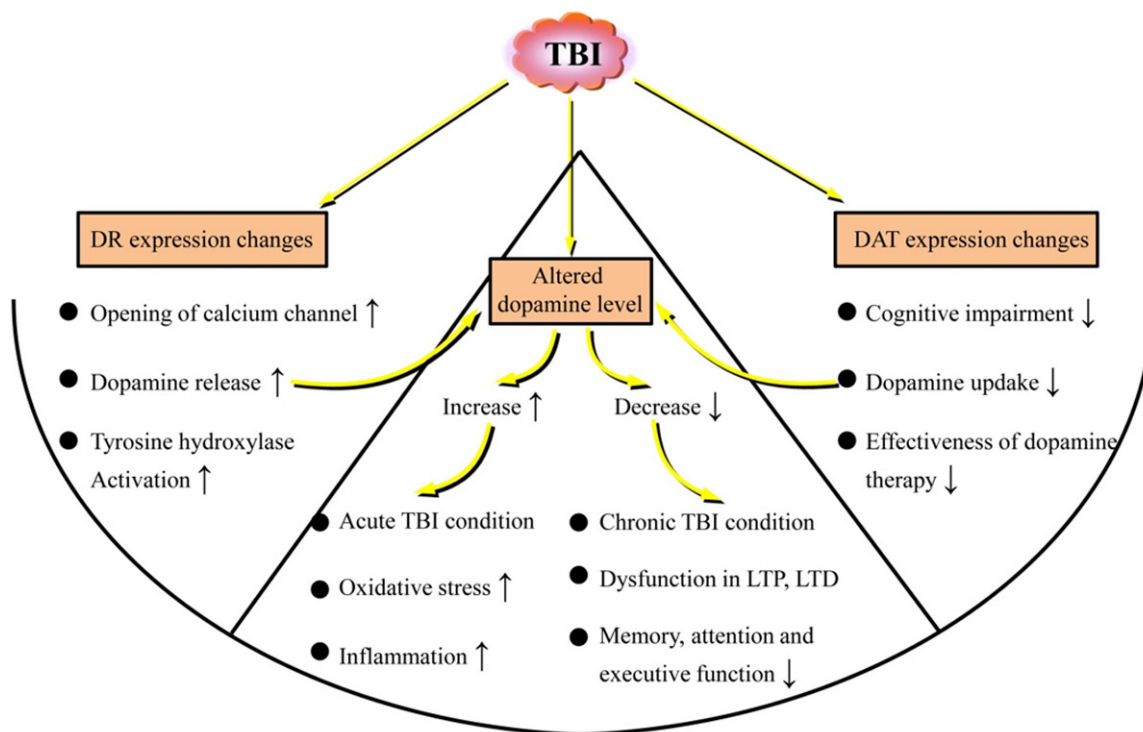
**Keywords:** Dopamine, traumatic brain injury, dopamine transporter, neuroprotection

## Introduction

Traumatic brain injury (TBI) is a major cause of death or disability worldwide. In the last 3 decades, various neuroprotective agents that could attenuate the downstream damaging events triggered by TBI have been explored. Although some drugs have demonstrated promising results in the preclinical stage, all have failed in large clinical trials [1]. Many of the neurological deficits that result from brain injury are caused by direct anatomical damage, but inhibition of chemical transmission also exerts important effects. These changes have been investigated and confirmed in epigenetic and behavioral studies [2, 3]. Among the neurotransmitter systems, dopamine pathways seem especially vulnerable to brain injury due to the anatomic properties of the dopaminergic system. Animal models of TBI show both dopaminergic cell loss and biochemical disturbances

of the dopaminergic system [4]. There is convincing evidence that dopamine dysfunction contributes to post-TBI deficits, while dopaminergic regulation could exert prominent neuroprotective effects.

Targeting dopamine signaling in TBI could be of great significance because dopamine impacts various brain regions, including the hippocampus [5, 6], striatum [7], and frontal cortex (FC) [8, 9]; damage in these regions has been associated with cognitive dysfunction in TBI. In addition, TBI has been associated with fluctuations in dopamine levels [10]. More importantly, the neuroprotective and therapeutic strategies that focus on the dopaminergic system have revealed great benefits, and the use of dopamine agonists has revealed benefits not only in preclinical experiments but also in clinical trials [11-13]. Thus, here we provide support for dopamine as a viable target in acute TBI, and this



**Figure 1.** Changes in dopamine and related alterations in dopaminergic systems induced by traumatic brain injury (TBI). TBI could cause altered dopamine release, dopamine receptor (DR) expression changes, and changes in dopamine transporter (DAT) expression in the brain. Changes in levels and expression of dopamine and related alterations, including DR and DAT in dopaminergic systems, could have a great impact on functional outcomes.

review focuses on the dopamine system related to brain injury.

**Alterations in dopaminergic systems following TBI**

Multiple brain regions are affected by TBI, including the FC [8, 9], hippocampus [5, 6], and striatum [7]. These three regions are particularly important because of their role in learning, memory, executive function and attention [14-18], and they could be impaired after TBI [19-23]. However, damage to brain tissue after TBI is not limited to discrete brain regions. Diffuse axonal injury in white matter tracts along with gray matter damage [24-27] further complicates the clinical presentation of TBI. The widespread disruption of neuronal projections has implications for all neurotransmitter systems, including dopamine. Whether depleted or at excessively high levels, dopamine can cause significant cellular dysfunction; thus, the changes in the levels of dopamine and related alterations in dopaminergic systems could have a great impact on functional outcomes (**Figure**

**1).** Potential strategies attenuating dopaminergic alterations could thus be of great significance for improving TBI treatment efficacy.

*Altered dopamine release following TBI*

Dopamine is involved in various dysfunctional processes caused by TBI. There is evidence that dopamine release is affected by TBI [28, 29], and this may contribute to various psychological disorders that are often observed [30, 31]. Dopamine release is associated with cognitive behavior [32]. In addition, several mechanisms induced by TBI that could affect neurotransmission, especially dopamine transmission, have been elucidated; these mechanisms involve neuroinflammation that is induced after the initial insult in TBI [33, 34] and play a critical role in secondary neurodegeneration [33]. The role that acutely released dopamine plays following TBI is complex (**Figure 1**). Whether the initial increase is neurotoxic or is an attempt to restore functional circuitry damaged by the mechanical insult is unclear [10]. A dramatic increase in dopamine within the central ner-

vous system (CNS) has multiple consequences, including increased oxidative stress and the induction of inflammatory signals, while a decrease in dopamine, which often occurs in chronic TBI conditions, has other consequences, such as dysfunction in long-term depression (LTD) and long-term potentiation (LTP) processes, as well as deficits in memory, attention and executive functions [10].

A major site of dopamine activity is the nucleus accumbens (NAC), which includes an inner core and outer shell with very different functions [29]. If variations in dopamine release patterns are related to symptoms of TBI, such as cognitive dysfunction that is impacted by different parts of the NAC, differences in dopamine physiology between the core and shell are likely to have important implications for the relevant clinical manifestations. However, the effect of TBI on stimulus-related dopamine dynamics in different regions of the NAC still is in need of further research. Intriguingly, Chen et al. [29] reported that TBI was associated with major changes in dopamine release in both the core and shell of the NAC that correlated with the severity of injury, with the core being somewhat more vulnerable to TBI-associated changes. Furthermore, their research revealed that the most significant alterations in dopamine dynamics occurred at 1-2 weeks after injury, with some recovery over the longer term. These electrochemical findings in NAC could clarify the mechanisms related to post-TBI psychological syndromes and support the modulation of dopaminergic mechanisms as clinical therapeutic strategies for TBI.

### *Dopamine receptor expression changes in TBI*

Dopamine can be synthesized at different places in the CNS and regulates cognition, emotion and various other physiological functions through binding to dopamine receptors [35]. Dopamine receptors can be generally divided into 5 subtypes, i.e., D1-D5 [36]. Based on the signal transduction mechanisms that are activated after binding of agonists to the different receptor subtypes, dopamine receptors have been classified as either D1-class receptors (D1 and D5), which are mainly distributed in the kidney, heart, and mesenteric tissue, or D2-class dopamine receptors (D2, D3, and D4), which are mainly distributed in the presynaptic adrenergic nerve endings and sympathetic gangl-

ia [37-41]. D1 and D5 receptors activate the  $G\alpha_{s/olf}$  family of G proteins to stimulate cAMP production by adenylate cyclase, while D2, D3, and D4 receptors couple to the  $G\alpha_{i/o}$  family of G proteins and inhibit adenylate cyclase activity [36].

During TBI, transient mechanical violence acts on the nervous system, which leads to neuronal hyperexcitability and the opening of calcium channels as well as the activation of dopaminergic neurons followed by dopamine release [42-45]. Tyrosine hydroxylase (TH) activity in neurons is enhanced by the activation of calcium channels, and the activation of TH accelerates dopamine synthesis by dopaminergic neurons, resulting in the accumulation of a large amount of dopamine [46, 47]. Thus, the activation of calcium channels could also impact dopamine levels. Interestingly, it has been confirmed that dopamine D1 receptor activity can exert modulatory effects on calcium channel currents [48]. Thus, activity of dopamine receptors themselves can also regulate the accumulation of dopamine. In addition, transient decreases in dopamine D1 receptor binding have been shown to occur immediately following injury [49] but do not persist chronically. The authors suggested that striatal dopamine D1 receptors were downregulated and then upregulated following isolated injury to the cerebral cortex. Overall, these data have indicated that in patients with TBI, the dopamine signaling pathways play an important role in brain injury and that dopamine receptors may also become novel targets for the treatment of brain injury [50].

### *Changes in dopamine transporter expression in the brain following TBI*

Dopamine neurotransmission relies in part on dopamine transporter (DATs), which are membrane proteins that transport dopamine from the synapse to the cytosol [51]. Monoamine oxidase (MAO) metabolizes dopamine in the cytosol into 3,4-dihydroxyphenylacetic acid [52]. Dopamine that is not metabolized by this process is taken up into vesicles by the vesicular monoamine transporter 2 (VMT2) and is recycled to maintain dopamine homeostasis [53]. DATs are mainly expressed in the substantia nigra (SN), retrorubral field (RRF), and ventral tegmental area (VTA) of the ventral midbrain [54]. Significantly, decreased DAT levels in the rat FC [55] and striatum [56] after TBI

have been found, and experimental studies have also demonstrated that TBI induces a loss of dopaminergic neurons in the SN in rats [4], suggesting that dopaminergic neurons in the SN are more vulnerable to TBI than neighboring neuronal populations. However, Shimada et al. [57] reported that there were no significant changes in DAT expression levels in the SN but found significantly decreased DAT expression in the RRF. Importantly, dopaminergic neurons are more important in the RRF than in the SN and VTA because the RRF cell group could be composed of the largest dopamine neurons [58].

Generally, various studies have demonstrated that DAT levels decreased continuously after TBI, and notably, that the rate at which DAT removes dopamine from the synapse could have a profound effect on dopamine levels in the cell. This is best evidenced by the severe cognitive deficits, hyperactivity and motor abnormalities exhibited by DAT knockout mice [59]. Therefore, the decreased levels of DAT expression after TBI could result in decreased dopamine neurotransmission in the brain. Since dopamine neurons in the RRF project to the amygdala, striatum, bed nucleus of the stria terminalis [60], and hippocampal formation [61], the decreased levels of expression of DAT in the RRF may also cause dysfunctions in these areas. Furthermore, decreased DAT expression levels may be related to the effectiveness of dopamine therapy in TBI patients, which is discussed further in the following text.

Interestingly, in a recent study, Jenkins et al. [62] demonstrated that striatal DAT abnormalities measured using  $^{123}\text{I}$ -ioflupane single-photon emission computed tomography (SPECT) are commonly observed following moderate/severe TBI. One-third of the SPECT scans were clinically reported as abnormal. These changes are a marker of reduced striatal dopamine. Their results suggested that these changes were due to the pattern of nigrostriatal tract damage produced by axonal injury. Compared with that in normal patients, cognitive impairment in patients with marked reductions in caudate DAT levels was greater, and similar cognitive impairments respond to dopaminergic treatments in other contexts. Therefore, DAT abnormalities following TBI may assist in treatment selection after TBI.

### **Cellular mechanisms regarding the neuroprotective effects of dopamine in TBI**

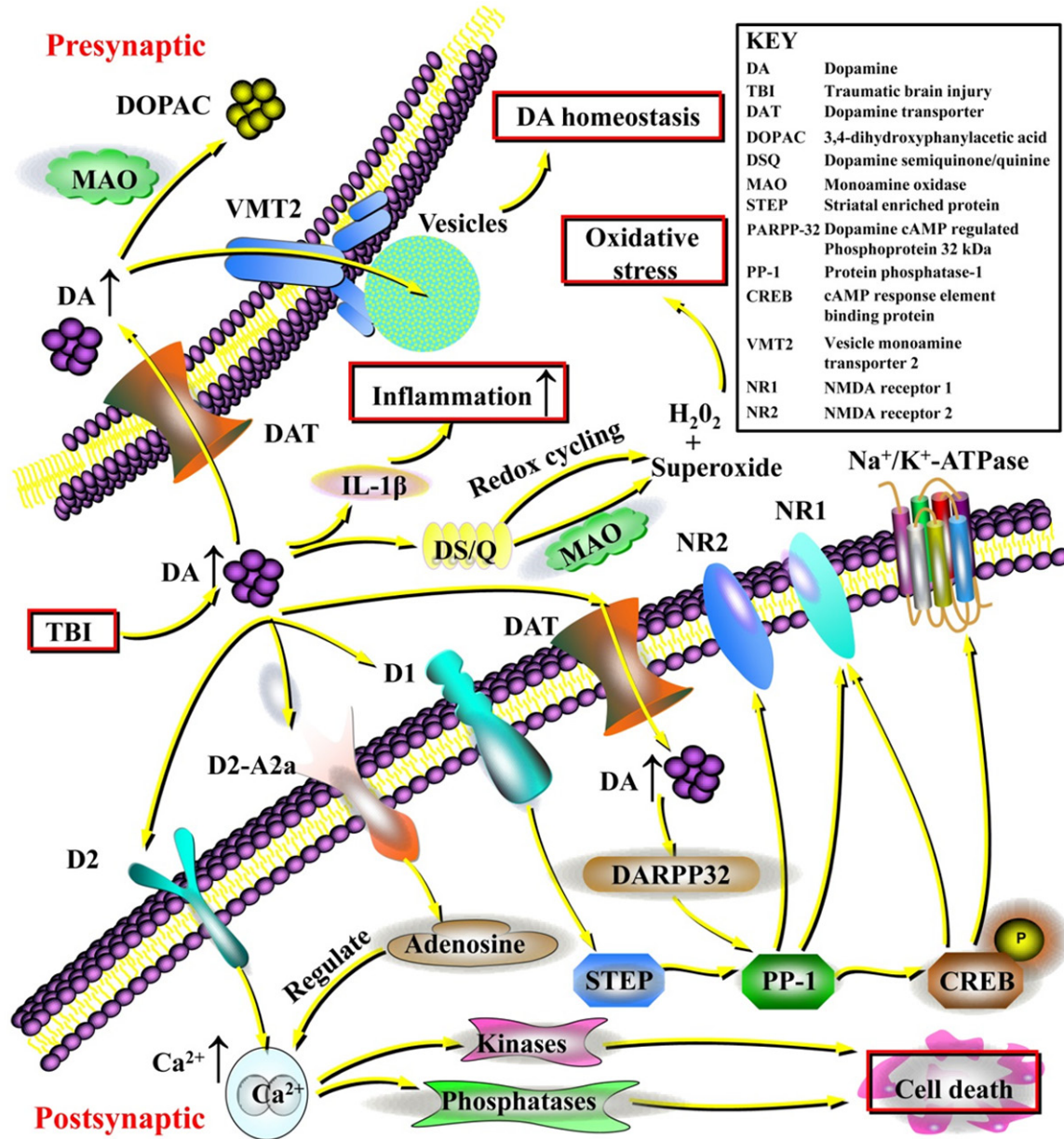
Dopamine is a critical neurotransmitter for the normal function of the hippocampus, FC, and striatum [63-65]. The contribution of dopamine to intracellular signaling molecules makes dopaminergic regulation essentially important for multiple neuroprotection strategies for TBI (**Figure 2**).

#### *Dopamine in cellular dysfunction*

Dopamine, similar to glutamate, can also be a potent excitotoxic agent [66]. For example, high levels of dopamine in the synaptic cleft can be rapidly oxidized to form dopamine semiquinone/quinone [67]. In addition, oxidized dopamine via MAO activity [68] or redox cycling [69] can induce the generation of hydrogen peroxide and superoxide causing significant oxidative stress. Furthermore, dopamine signaling at the dopamine D2 receptor can induce increases in intracellular  $\text{Ca}^{2+}$  release and activation of calcium-dependent kinases and phosphatases, which is important for cell death signaling [70-72]. Animal models of TBI consistently result in widespread excitotoxic damage and increased amounts of oxidative stress in a number of different brain regions [73, 74]. The initial increases in dopamine observed post TBI may promote excitotoxic disruption of and oxidative damage to the function of dopaminergic cells [56]. Interestingly, depleting dopaminergic projections into the striatum prior to the ischemic insult was found to be neuroprotective [75], indicating that dopamine could be neurotoxic.

Following TBI, there are known alterations in intracellular  $\text{Ca}^{2+}$  release [76, 77], glutamatergic receptor function [78, 79], and alterations in the function of  $\text{Na}^+/\text{K}^+$ -ATPase [80]. In addition, levels of excitatory amino acids and acetylcholine are markedly increased acutely in injured rats [81], and metabolic activity is also increased, resulting in adenosine triphosphate (ATP) depletion [82]. There are also decreases in both N-methyl-D-aspartic acid receptor (NMDA) NR1 and NR2 subunit expression a few hours after TBI [83]. Intriguingly, dopamine exerts an important effect on the regulation of  $\text{Na}^+/\text{K}^+$ -ATPase, calcium release, and the NMDA receptor through dopamine cAMP-regulated phosphoprotein 32 kDa (DARPP-32) and protein phosphatase-1 (PP-1) [84, 85]. Dopami-





**Figure 2.** The contribution of dopamine to intracellular signaling and the essential neuroprotective effects of dopaminergic regulation following traumatic brain injury (TBI). Excessive dopamine could exert potent excitotoxic effects, inducing the generation of hydrogen peroxide ( $H_2O_2$ ) and superoxide causing significant oxidative stress. In addition, dopamine can act as a potent inflammatory agent inducing inflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ), and dopaminergic regulation can potentially be important for reducing inflammation within the central nervous system (CNS). Excessive dopamine that is not metabolized by monoamine oxidase (MAO) could be recycled into vesicles by the vesicular monoamine transporter 2 (VMT2), maintaining dopamine homeostasis. Furthermore, the cellular mechanisms regarding the neuroprotective effects of dopamine in TBI have also been revealed. Dopamine exerts important effects on the regulation of  $Na^+/K^+$ -ATPase,  $Ca^{2+}$  release, and the N-methyl-D-aspartic acid receptor (NMDA) receptor through dopamine, cAMP-regulated phosphoprotein 32 kDa (DARPP-32) and protein phosphatase-1 (PP-1). Specifically, dopamine acting on D1 receptors can modify the activity of striatal enriched protein (STEP), which contributes to PP-1 activity. PP-1 also regulates nuclear transcription through cAMP response element-binding protein (CREB) phosphorylation and plays an important role in the phosphorylation of the NMDA NR1 subunit and the  $Na^+/K^+$ -ATPase. Dopamine signaling at the dopamine D2 receptor can induce increases in intracellular  $Ca^{2+}$  release and activation of calcium-dependent kinases and phosphatases, which is important for cell death signaling. Dopamine also forms a tight signaling relationship with adenosine via dopamine D2/adenosine A2a receptor interactions that can directly control intracellular  $Ca^{2+}$  release. Clarifying these dopaminergic signaling pathways could help identify promising therapies targeting dopamine and direct attention to this neurotransmitter for clinical applications.

nergic signaling pathways can modify the phosphorylation of DARPP-32, which is followed by alterations in downstream PP-1 activity [85]. In hippocampal neurons, dopamine acting on D1 receptors can modify the activity of striatal enriched protein (STEP), which contributes to PP-1 activity [86, 87]. PP-1 also regulates nuclear transcription through cAMP response element-binding protein (CREB) phosphorylation [88] and plays an important role in the phosphorylation of the NMDA NR1 subunit and Na<sup>+</sup>/K<sup>+</sup>-ATPase [87, 89]. In addition to effects on PP-1, dopamine forms a tight signaling relationship with adenosine via dopamine D2/adenosine A2a receptor interactions that can directly control intracellular calcium release [90, 91].

### *Dopamine in CNS inflammation*

TBI causes a time-dependent upregulation of various genes during the postinjury period that include inflammatory cytokines such as interleukin 1 (IL-1), tumor necrosis factor (TNF), cyclooxygenase (COX) 1 and 2 and prostaglandin (PG) synthases. These may contribute to inflammation in the brain [92]. Thus, the neurodegenerative changes after TBI may be associated with inflammatory responses [93]. Moreover, significant decreases in TH-positive expression in the surviving dopaminergic neurons of the SN pars compacta (SNpc) and increased  $\alpha$ -synuclein accumulation in the inflammation-infiltrated SN of rats exposed to chronic TBI were shown [34]. These phenomena may be one of the critical mechanisms by which dopamine transmission is impaired after TBI [33]. Strategies to reduce neuronal inflammation in TBI have provided benefits in functional outcomes [94-96]. However, the potential neuroprotective role of inflammatory cells cannot be ignored, and direct inhibition of inflammation may cause various side effects [97, 98].

Dopamine can act as a potent inflammatory agent within the CNS. It is known that excessive dopamine levels could induce a proinflammatory environment [99], and inflammatory factors could be further augmented by dopamine supplementation, which can further increase interleukin-1 $\beta$  (IL-1 $\beta$ ) production [100, 101]. Intriguingly, in TBI, blocking IL-1 $\beta$  can be beneficial [94]. There is also the recognized vulnerability of dopaminergic neurons to the inflammatory cascade [102-104]. It has also been shown

that drugs with dopaminergic action can reduce inflammation within the CNS [105]. This finding suggests that while endogenous dopamine can activate inflammatory pathways, activation of dopamine receptors with therapeutics may still provide reductions in inflammation. This dual nature of dopaminergic signaling also demonstrates the dopaminergic signaling complexities that need to be better understood as therapies targeting dopamine move towards clinical application.

### **Experimental evidence for the neuroprotective effects of dopamine against TBI impairments: beneficial outcomes**

Multiple studies have demonstrated that cerebral autoregulation is absent or impaired in significant numbers of patients after TBI, even when values of cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) were normal [106]. When autoregulation is impaired, decreases in CPP result in decreases in CBF; in moderate/severe TBI, such decreases in CBF may reach ischemic levels or lead to severe stroke, further augmenting various secondary injuries. Many retrospective studies have observed that impaired cerebral autoregulation could be associated with worsened cognitive outcomes (Glasgow Outcome Scale) [107-109]. In addition, previous research has indicated that phenylephrine (Phe), norepinephrine (NE), and epinephrine (EPI) all prevented reductions in CBF associated with fluid percussion injury (FPI) and limited neuronal cell necrosis in hippocampal areas CA1 and CA3 as a function of age and sex [110, 111]. While cognition depends on more than the hippocampus, and cognitive testing was not performed in these studies, such results do suggest that support with vasoactive agents may affect cognitive outcomes after TBI.

Previously, it has been shown that dopamine equally protected cerebral autoregulation in male and female newborn pigs [112], indicating that dopamine improves outcomes irrespective of age and/or sex. However, other recent studies using different vasoactive agents have observed conflicting effects, building the argument for use of a precision medicine approach in the treatment of TBI. For example, Phe and NE have been shown to worsen cerebral autoregulation and histopathology in male but not female newborn piglets and male and female

juvenile pigs after FPI [113, 114]. In contrast, EPI prevents impairment of cerebral autoregulation and histopathology in male and female newborn and female juvenile pigs but not male juvenile pigs after FPI [111].

Since dopamine prevents impairments in cerebral autoregulation in both ages and sexes, dopamine should be recommended for the promotion of cognitive improvement after TBI independent of age and sex. A recent study [114] has indicated that dopamine protects autoregulation and prevents hippocampal neuronal cell necrosis via blocking ERK after brain injury in both male and female juvenile pigs. These results were novel in that they showed that dopamine was the only vasoactive agent studied thus far that improved outcome after TBI in both ages and sexes, and the authors suggested that dopamine should be explored as the vasoactive agent of choice in the treatment of pediatric TBI irrespective of age and sex for improving outcomes. However, a limitation was that histology was performed at an early time point; differences between treatment groups and sexes may disappear as more neurons die beyond the early time point. Therefore, additional studies will be needed to determine if the prevention of the loss of neurovascular unit integrity durably improves cerebral hemodynamics and cognitive function after pediatric TBI.

### **Influence of dopamine-related genes on neurobehavioral recovery after TBI**

In clinical practice, it is common to observe different functional outcomes in individuals with similar degrees of TBI. Similarly, individual responses to medications can also vary enormously. These differences suggest that host factors may play an important role in the outcomes. Host genotype might be one such factor. Currently, although some important preliminary findings have been found [115, 116], which will be discussed in the following text, our knowledge of the role of genetic factors in response to trauma and recovery from trauma, including reactivity to drugs, is limited and more research is needed.

Dopamine could be important for plasticity by enhancing synaptogenesis and neural sprouting [117], for recovery of motor function after TBI [118], and for cognitive reserve and the

treatment of cognitive deficits after TBI [119]. Thus, polymorphisms in genes involved in the dopaminergic system could have great potential to influence behavioral outcomes after TBI. Candidate genes include those coding for dopamine receptor subtypes, dopamine reuptake (DAT), and dopamine metabolism (catechol-O-methyl transferase or COMT) [120]. Interestingly, positron emission tomography (PET) studies have shown changes in striatal D2 binding following working memory training [121], and lower dopamine D2 receptor densities have been associated with better motor sequence learning in healthy adults [122]. Recently, children and adolescents who were carriers of ANKK1 rs1800497 demonstrated greater improvements during working memory training than those who were not carriers [123]. Similarly, variation in SLC6A3 influenced improvements in working memory following cognitive training in preschool and school-age children [124, 125]. Taken together, these studies suggest that the ANKK1 and SLC6A3 genes may provide higher cognitive [123] or neural [126] plasticity that may be especially relevant to recovery from injury to the brain.

The study of Treble-Barna et al. [127] was the first to provide preliminary evidence for the influence of variation in dopamine-related genes on neurobehavioral recovery following TBI in children. They examined the association of dopamine-related genes with short- and long-term neurobehavioral recovery in children who had sustained early childhood TBI. Genetic variation within the SLC6A3 (rs464049 and rs460000) gene was found to be associated with neurobehavioral recovery trajectories over time following TBI. In addition, genetic variation within ANKK1 (rs1800497 and rs2734849) and SLC6A3 (rs464049, rs460000, and rs1042098) was also associated with short- and long-term neurobehavioral recovery following TBI. The authors demonstrated that genetic variation in genes involved in D2 receptor (ANKK1) and DAT (SLC6A3) expression and density plays a role in neurobehavioral recovery following TBI.

The effect of genetic variation on treatment outcomes, including potential responses to drugs, is less advanced. However, it is encouraging that even with relatively small sample sizes, several groups have found genetic effects that influence cognitive outcomes. Larger sample sizes are needed to replicate these findings.



### **The clinical effectiveness and therapeutic significance of dopamine agonists for improving behavior after TBI**

There has been longstanding evidence that dopaminergic therapy improves neuropsychiatric outcomes in TBI and non-TBI conditions. However, until recently, there has not been a rigorous evaluation of these findings in double-blind RCTs. To date, much of the evidence has come from case reports, case series or open-label trials. To date, only six studies were found to provide data on patients who received dopaminergic therapy [30, 128-131], including the four drugs amantadine, levodopa, bromocriptine and rotigotine (**Table 1**). There is a need for larger prospective, double-blind RCTs with these medications using standardized criteria and outcomes to fully understand their effectiveness in this patient group.

Amantadine is usually prescribed as an antiparkinsonian agent, as a treatment for neuroleptic-induced extrapyramidal symptoms, and as an antiviral agent. Amantadine appears to be a safe and effective means of reducing irritability and aggression among individuals who have had TBI for greater than 6 months' duration and have sufficient creatinine clearance [30].

Levodopa has long been used for the treatment of Parkinson's disease (PD). Lokk et al. [132] demonstrated that patients administered levodopa showed improvements in stroke severity over time. There were no side effects reported, and their findings will redirect attention to the clinical benefits of this type of drug treatment in rehabilitation. Future studies should address issues of optimal therapeutic windows and dosage of the medication as well as identify those patients with stroke who are likely to benefit from this treatment.

Bromocriptine, a direct dopamine agonist affecting primarily D2 receptors, also seems to have activity related to specific executive functions and attentional abilities in both animal and human studies. Whyte et al. [130] indicated that bromocriptine at a dose of 5 mg given twice a day to individuals with attentional complaints after TBI did not enhance attentional skills and may have been associated with an excess of adverse events. It is not clear whether intermittent dosing or lower doses might be beneficial.

Rotigotine has high affinity for the D1 receptor compared with many other available oral dopamine agonists. Gorgoraptis et al. [131] explored whether the dopamine agonist rotigotine would have a beneficial effect on hemispatial neglect in stroke patients in a double-blind, randomized, placebo-controlled experiment. The authors suggested a beneficial role of dopaminergic modulation on visual search and selective attention in patients with hemispatial neglect following stroke.

In addition, there could also be many dopamine agonists that have not been explored in patients. For example, methylphenidate (MPH) treatment in experimental models demonstrated cognitive benefit after cortical impact injuries [133-135]. Amphetamine (AMPH) use in experimental models of TBI and selective cortical injury models has also been shown to accelerate recovery [136-142]. These dopamine agonists could be of potential therapeutic effect for TBI patients, although no clinical data have been reported.

However, the side effects of dopamine-related treatment modalities in TBI should also be considered. Contrasting effects of dopamine therapy have been shown in TBI animal models. Worsening of the brain swelling processes subsequent to the effects of vasopressor therapy in a clinical setting needs to be more carefully evaluated [143]. There are various molecular changes in TBI with no clear-cut therapies available. Clarification of these molecular changes in the dopamine system in TBI may lead to novel therapeutic approaches in the near future.

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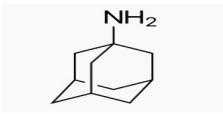
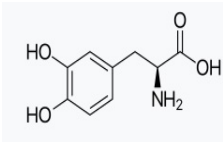
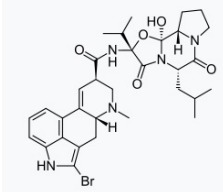
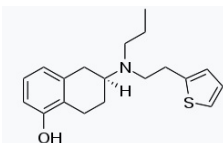
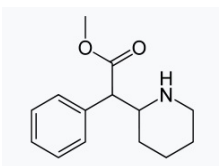
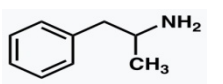
### **Disclosure of conflict of interest**

None.



## Dopamine in traumatic brain injury

**Table 1.** Summary of clinical and experimental studies involving dopamine agonists for improving TBI outcomes

Drug	Clinical data or experimental data	Chemical structure	Administration	Key findings/Objectives	Side effects	Reference
Amantadine	Clinical data		Oral amantadine hydrochloride as a single agent	Amantadine 200 mg daily appears a safe and effective means of reducing irritability and aggression among individuals with TBI greater than 6 months' duration and sufficient creatinine clearance.	Tremors and shakes (5%); Change in appetite (11%); Gastrointestinal (8%); Aches and pains (11%); Disoriented (5%); Seizure (3%)	Schneider et al. 1999; Meythaler et al. 2002; Hammond et al. 2014
Levodopa	Clinical data		Treatment of levodopa combined with physiotherapy	Patients having levodopa in combination with physiotherapy showed a stroke severity improvement over time.	No side effects reported	Lokk et al. 2011
Bromocriptine	Clinical data		Oral bromocriptine as a single agent	Bromocriptine in a dose of 5 mg, given twice a day to individuals with attentional complaints after TBI, does not seem to enhance attentional skills.	Few events were reported, and none of the adverse effects seemed to be related to bromocriptine	Whyte et al. 2008
Rotigotine	Clinical data		Rotigotine transdermal patches as a single agent	Rotigotine could be beneficial for visual search and selective attention in patients with hemispatial neglect following stroke.	Fatigue (25%); Topical skin reaction (6%); Nausea (31%); Vomiting (6%); Diarrhoea (13%)	Gorgoraptis et al. 2012
MPH	Experimental data		Daily injections of 5 mg/kg i.p. MPH as a single agent for 14 days following TBI	Chronic MPH treatment facilitates improvement of spatial learning acquisition and enhances striatal dopamine neurotransmission after experimental TBI.	None reported	Kline et al., 1994; Kline et al., 2000; Wagner et al., 2009
AMPH	Experimental data		Injections of 2 mg/kg dose of amphetamine sulfate as a single agent on days 2 and 5 following TBI	A short course of amphetamine treatment can enhance neuronal plasticity when appropriately linked with rehabilitation, thus resulting in improved motor recovery after TBI.	None reported	Feeney et al., 1981; M'Harzi et al., 1988; Hovda et al., 1989; Queen et al., 1997; Dhillon et al., 1998; Chudasama et al., 2005; Ramic et al., 2006

Abbreviations: TBI: Traumatic brain injury. MPH: Methylphenidate, AMPH: Amphetamine.

## Abbreviations

TBI, traumatic brain injury; FC, frontal cortex; NAC, nucleus accumbens; CNS, central nervous system; MAO, monoamine oxidase; DAT, dopamine transporter; VMT2, vesicular monoamine transporter 2; SN, substantia nigra; RRF, retrorubral field; VTA, ventral tegmental area; DARPP-32, dopamine cAMP regulated phosphoprotein 32 kDa; PP-1, protein phosphatase-1; STEP, striatal enriched protein; CREB, cAMP response element binding protein; IL-1, interleukin 1; TNF, tumor necrosis factor; COX, cyclooxygenase; PG, prostaglandin; CPP, cerebral perfusion pressure; CBF, cerebral blood flow; Phe, phenylephrine; NE, norepinephrine; EPI, epinephrine; FPI, fluid percussion injury; PET, positron emission tomography; MPH, methylphenidate; AMPH, amphetamine.

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