Targeting Dopamine in Acute Traumatic Brain Injury

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Abstract: In addition to the initial mechanical damage, traumatic brain injury (TBI) induces a series of secondary insults, such as, but not limited to, excitotoxicity, metabolic disruption, and oxidative stress. Neuroprotective strategies after TBI have traditionally focused on cellular preservation as the measurable endpoint although multiple lines of evidence indicate that even with significant neuronal sparing deficits remain at both the cellular and behavioral level. As such, the development of therapies that can effectively confer both neuronal sparing and post-injury functional benefit is critical to providing the best treatment options for clinical TBI. Targeting dopaminergic signaling pathways is a novel approach in TBI that provides benefits to both neuronal survival and functional outcomes. Dopamine, like glutamate, can cause oxidative stress and significant cellular dysfunction when either depleted or over-expressed, and also plays an important role in central nervous system inflammation. The purpose of this review is to discuss dopamine in acute TBI and the role that dopaminergic therapies have as neuroprotective strategies.

Keywords: Dopamine, traumatic brain injury, neuroprotection, plasticity.

INTRODUCTION

Traumatic Brain Injury: The Problem

Traumatic brain injury (TBI) is a heterogeneous and complex condition composed of acute, sub-acute, and chronic pathologies [1, 2]. Animal models of brain injury, including controlled cortical impact (CCI) [3, 4] and fluid percussion (FP) [5], have provided insight into the cellular and mechanical mechanisms of central nervous system (CNS) dysfunction and cell death. These insights afford the opportunity for the examination of valuable treatment strategies [6, 7] and a better understanding of persistent deficits [4, 5, 8-10]. Unfortunately, many of the neuroprotective strategies employed in experimental TBI research have not translated successfully to the clinic [11, 12]. Potential reasons for poor translation of basic research results to the clinic include, but are not limited to, 1) the complexities of multi-system traumas typically seen in clinical settings [13, 14], 2) a compromised blood brain barrier [15, 16], 3) potential drug toxicities and side effects [17, 18], and 4) incomplete preclinical evaluations. Strategies that target glutamatergic excitotoxicity acutely to provide neuronal sparing have proven particularly difficult given the important function of glutamate signaling in cellular potentiating, learning, and memory [19-22]. To address these issues, multiple studies have utilized paradigms designed to inhibit cell death pathways with the intent of reducing the level of acute neuronal loss after injury [23, 24]. However, this strategy has often met with varied success due to persistent cellular dysfunction even when significant cell sparing is present [17, 25]. The failure of these paradigms indicates that different approaches for the treatment of acute TBI are needed. The benefits of dopaminergic (DAergic) targeted strategies are well-established in rehabilitation and chronic treatment paradigms [24, 26, 27]. Here we provide support for dopamine (DA) as a viable target in acute TBI.

Acute Alterations in Dopaminergic Systems Following TBI

Multiple brain regions are affected by acute TBI including, but not limited to, the hippocampus [28, 29], frontal cortex (FC) [5, 30], and striatum [31]. These three regions are particularly important because of their role in attention, executive function, learning, and memory [32-36]. Each of these four cognitive realms can be significantly impaired after TBI [37-42]. While the brain generally functions through the interaction of multiple regions, the hippocampus, FC, and striatum are unique in that DA, through interactions with glutamate, is required for neuronal potentiation in each area [43-46]. However, tissue damage after TBI is not limited to discrete brain regions. Diffuse axonal injury in white matter tracts along with gray matter damage [47-50] further complicates the clinical presentation of acute brain injury. The widespread disruption of neuronal projections has implications for all neurotransmitter systems, including DA.

Loss of DAergicinnervating fibers from the ventral tegmental area and substantia nigra alter synaptic structure and dendritic complexity within the striatum and FC [51-53]. Furthermore, both antipsychotic and CNS stimulant drugs that exert activities on DA terminals have been shown to partially improve changes in synaptic and dendritic structure in multiple disorders including Parkinson’s disease (PD), attention deficit hyperactivity disorder, and schizophrenia [54-56]. In particular, chronic treatment with CNS stimulants such as amphetamine and methylphenidate (MPD) has been...
shown to increase dendritic complexity and enhance synaptic plasticity in the striatum and FC [57, 58]. While TBI shares commonalities with other DAergic-mediated disorders in terms of cognitive dysfunction and the associated benefits gained by stimulant therapy, there have been few detailed studies of TBI-induced changes in DA structure. What is known is that TBI increases tyrosine hydroxylase (TH), the rate-limiting enzyme in DA synthesis, in the rat frontal cortex at 28 days post-injury [59]. The increase in TH protein most likely enhances DA synthesis via the phosphorylation of TH, which effectively increases its activity and is also upregulated after TBI [60]. In contrast, DA beta hydroxylase (DBH) protein, which is the enzyme that converts DA to other catecholamines, is not altered after TBI suggesting that the increase in TH predominantly affects DAergic axons [59]. Modest increases in TH protein after severe TBI have also been observed in the striatum with a similar temporal profile [61]. Changes in expression of TH protein suggest an alteration in DA-relevant structures within the FC and striatum that provides a viable synergistic target in addition to molecular signaling events known to be altered in DA systems after TBI.

Following experimental TBI, catecholamine systems are dysregulated [62-65]. Transient increases in DA levels have been appreciated acutely and sub-acute/y in a variety of different brain regions [62] including the striatum [64, 65] and frontal cortex [65]. Beyond DA tissue levels, there have also been recognized increases in striatal DA metabolism acutely as measured by dihydroxyphenylacetic acid (DOPAC)/DA ratios [65]. Elevations in catechol-O-methyl-transferase expression, an enzyme involved in the deactivation and breakdown of multiple catecholamines, including DA, begin as early as 24 hours after TBI and persist for up to 14 days in the microglia of the injured hippocampus [66]. Although DA levels increase acutely in many brain regions, TH activity is upregulated at chronic time points in the prelimbic and infralimbic cortices [60], as well as in the substantia nigra and FC [59, 61]. The increase in TH activity at later time points is consistent with data showing reduced levels of DA in the injured cortices 2 weeks post-injury [64]. Alterations in DA receptor systems have further elucidated this dissociation between acute and chronic DAergic responses to TBI. Transient decreases in DA D1 receptor binding have been shown to occur immediately following injury [67], but do not persist chronically.

**Implications of Acute Dopamine Increases Following TBI**

**Dopamine and Cell Death**

DA is a critical neurotransmitter for the normal function of the hippocampus, FC, and striatum [68-70]. It is particularly important for both long-term potentiation (LTP) and long-term depression (LTD) [71-73]. However, like glutamate, DA is carefully regulated by the CNS and alterations can lead to significant cellular dysfunction and/or death [74]. Dysregulation of DA levels or death of DAergic neurons that induce low DA states can lead to some of the symptoms of schizophrenia and PD [75, 76]. Conversely high levels of DA are also implicated in symptoms associated with schizophrenia and cause significant dysfunction in working memory (WM) and learning [77, 78].

DA, like glutamate, can also be a potent excitotoxic agent [79]. For example, high levels of DA in the synaptic cleft can be rapidly oxidized to form DA semiquinone/quinine [80]. In addition, oxidized DA via monoamine oxidase (MAO) activity [81] or redox cycling [82] can induce the generation of hydrogen peroxide and superoxide causing significant oxidative stress. 6-hydroxydopamine (6-OHDA) has been used as a classical neurotoxin in PD as injection into sensitive brain regions can lead to cellular death within a few days [83, 84]. Furthermore, DA signaling at the DA D2 receptor can induce increases in intracellular Ca$^{2+}$ release and activation of calcium dependent kinases and phosphatases important for cell death signaling [85-87]. Animal models of TBI consistently produce widespread excitotoxic damage and increased amounts of oxidative stress in a number of different brain regions [88, 89]. DAergic fibers have been shown to modulate striatal glutamatergic excitotoxicity [90, 91]. The initial increases in DA observed post-TBI may precipitate excitotoxic disruption and oxidative damage to DAergic cellular function that leads to the observed alterations in DA kinetics and decreased evoked DA release at later time-points [92]. Furthermore, following ischemia there is a 500 fold increase in DA concentrations within the striatum [93]. Striatal ischemia has also been appreciated following experimental TBI [31]. Interestingly, depleting DAergic projections into the striatum prior to the ischemic insult is neuroprotective [94], suggesting that DA can be neurotoxic.

**Dopamine and Acute Cellular Dysfunction**

Following TBI there are known alterations in intracellular calcium release [95, 96], glutamatergic receptor function [23, 97], and alterations in the function of Na/K ATPase [98]. Levels of excitatory amino acids (e.g. glutamate and aspartate) and acetylcholine are markedly increased acutely in injured rats [99]. Metabolic activity is also increased resulting in adenine triphosphate (ATP) depletion [100]. In hypoxia-ischemia, there is increased expression and phosphorylation of the N-methyl-D-aspartatic acid receptor (NMDA) NR1 subunit at the DA dependent serine-897 site [101]. At 6-12 hours following TBI there is a recognized decrease in both NR1 and NR2 subunit expression [102]. DA plays an important role in the regulation of the Na/K ATPase, cellular metabolism, calcium release, and the NMDA receptor through dopamine cAMP regulated phosphoprotein 32 kDa (DARPP-32) and protein phosphatase 1 (PP-1) [103, 104]. DAergic and glutamatergic signaling pathways intersect within the FC and striatum to modify the phosphorylation of DARPP-32, thereby altering downstream PP-1 activity [104]. In hippocampal neurons, DA acting on D1 receptors can modify the activity of striatal enriched protein (STEP), which contributes to PP-1 activity within the hippocampus [105, 106]. PP-1 regulates nuclear transcription through cAMP response element binding protein (CREB) phosphorylation [107] and also plays a role in the phosphorylation of the Na/K ATPase and the NMDA NR1 subunit [106, 108]. In addition to the affect on PP-1, DA forms a tight signaling relationship with adenosine via D2-A2a receptor interactions that can directly control intracellular calcium release [109, 110].

The DARPP-32 protein is directly acted upon via calcineurin. Calcineurin activity helps regulate the
phosphorylation of DARPP-32 at the threonine-34 site contributing to its control over PP-1 activity [103]. The induction of calcineurin activity [111] following TBI and the alterations in calcineurin subunit distribution [112, 113] make DA a potential key contributor to therapeutic interventions that act through calcineurin activation or inhibition.

The contribution of DA to intracellular signaling molecules within the hippocampus, FC, and striatum places DAergic regulation at the center of multiple neuroprotection strategies and contributes to the promising future of DAergic therapies for acute dysfunction following TBI.

**Dopamine and CNS Inflammation**

Strategies to reduce neuronal inflammation in TBI have provided benefits in neuronal sparing and functional outcomes [114-116]. However, difficulties remain due to concerns over the potential neuroprotective role of inflammatory cells and worries over what side effects direct inhibition of inflammation may cause [117, 118].

DA can act as a potent inflammatory agent within the CNS. In PD it has long been known that excessive DA or glutamate can induce a pro-inflammatory environment [119]. Inflammatory factors are further augmented in PD by L-DOPA supplementation, which can further exacerbate ERK activation and increase interleukin-1β (IL-1β) production [120, 121]. In TBI, blocking IL-1β is beneficial [114]. There is also recognized vulnerability of DAergic neurons to the inflammatory cascade [122, 123], which may be partially explained by the fact that microglia possess DA receptors that appear to stimulate migration and activation to DAergic brain regions [124]. It has also been shown that drugs with DAergic action can reduce inflammation (e.g. bupropion) within the CNS [125]. This suggests that while endogenous DA can activate inflammatory pathways, activation of DA receptors with therapeutics may still provide reductions in inflammation. This dual nature of DAergic signaling also demonstrates the complexities of DAergic signaling that need to be better understood as therapies targeting DA move towards clinical application.

**Targeting Dopamine Directly: Benefits to Outcome**

Clinical studies concerning DAergic agonists traditionally have examined DA enhancement therapies in the chronic or recovery phases after TBI. MPD, a DA transporter inhibitor, has been shown to benefit memory and attention in TBI patients when administered chronically [126]. The administration of amantadine hydrochloride (AMH) [127] and bromocriptine [128] during the recovery phase have also demonstrated improved retention in cognitive outcomes. Few studies have examined the clinical effectiveness of providing DA enhancement therapies acutely or sub-acutely (i.e. within days to weeks) after TBI, but of those that have been conducted, the results are promising. For example, providing MPD within the first month of injury improves recovery of attention and memory [129]. Because of its action on multiple catecholamines including DA [130, 131] AMH has received attention as an acute therapeutic. Specifically, the administration of AMH within the first week of TBI reduces patient agitation [132], improves the Glasgow coma score [133], and decreases measures of lipid peroxidation [134].

**Experimental Evidence: Dopamine Agonists**

The majority of experimental studies examining the effectiveness of DAergic therapies following TBI have utilized chronic administration paradigms. In most cases the treatments began within the first day of injury and continued with daily administrations until the completion of behavioral assessments (i.e. 21 days). The direct affects of acute administration are therefore unclear. However these studies provide compelling evidence for targeting DAergic systems in an acute phase.

MPD has demonstrated neuroprotection against the neurotoxic effects of methamphetamine and perhaps also Parkinson's [135]. Additionally, experimental models utilizing a MPD treatment paradigm demonstrated cognitive benefit after either cortical ablation or cortical impact injuries [136, 137]. Specifically, a single administration of MPD followed by significant symptom relevant experience (i.e. beam walking experience) enhanced recovery of motor function following sensorimotor cortex lesions [136]. Moreover, daily MPD treatments beginning as late as 24 hours after TBI in rats reveal significantly less spatial memory performance deficits vs saline treatment [137]. Daily treatment with MPD (5 mg/kg) after cortical impact injury resulted in improved DA overflow and Vmax compared to controls [138]. These data suggest that potential mechanisms for the benefits observed with MPD after TBI include restoration or improvement of DA synthesis and/or release of DA from DAergic terminals.

Amphetamine (AMPH) use in experimental models of TBI and selective cortical injury models has also been shown to accelerate recovery. The positive benefits of AMPH have been reported in FPI [139] and selective lesion studies [140-143]. AMPH treatment has been shown to reduce the accumulation of free fatty acids and lactate in the cortex and hippocampus following FPI [139] and attenuate decreases in cerebral glucose utilization [144]. Moreover, AMPH may produce benefits through its ability to induce hippocampal brain derived neurotrophic factor following brain injury [57]. This is not surprising given that AMPH treatment is known to induce dependent plasticity and synaptogenesis [54] and has been strongly linked to plastic alterations following brain injury [145, 146].

An important caveat to the AMPH studies is that while AMPH increases the levels of all monoamines [147], the beneficial effects of AMPH on motor recovery have only been reproduced following intraventricular administration of norepinephrine [148]. This finding does not rule out a positive role for DA facilitation with AMPH treatment on other cognitive processes, but simply suggests that DA-mediated benefits on motor recovery may not be due simply to increases in DA release. Support for this assertion comes from studies showing that the DA receptor antagonist, haloperidol, blocks the beneficial effects of AMPH treatment [149, 150].

Experimental use of AMH has also shown benefit following TBI. Daily treatment with AMH (10 mg/kg) showed significant improvements in spatial memory performance compared to saline treated controls [151].
Bromocriptine, a specific D2 receptor agonist, has demonstrated neuroprotective effects against glutamate induced toxicity in rat cortical neurons [152]. Treatment with bromocriptine (5 mg/kg) after cortical injury enhanced both WM and reference memory in a Morris water maze task [153]. A follow-up study [154] demonstrated that bromocriptine-treated rats exhibited spatial learning and also displayed increased hippocampal neuronal protection following TBI compared to vehicle-treated controls. Bromocriptine has also been shown to reduce lipid peroxidation, a measure of oxidative damage [154].

To Antagonize or Not to Antagonize

Unfortunately, there remains some ambiguity regarding the benefits of DAgergic antagonists in ischemic and TBI conditions. In an ischemic insult both DA D1 receptor agonists and antagonists have shown protection [155, 156] as have agonists and antagonists of DA D2 receptors [157, 158]. There remains a similar concern over the use of DA antagonists following TBI as there is with glutamatergic antagonists. Because DA is necessary for both LTP and LTD, which are cellular events required for learning and memory, substantially antagonizing DAgergic signaling may worsen outcomes. This is substantiated in the TBI literature by studies showing that the antipsychotics risperidone and haloperidol, both of which act as D2 receptor antagonists, worsen cognitive outcomes in rats when provided once daily for 19 days beginning 24 hours after cortical impact injury [6, 159].

Studies have also shown positive improvements in WM and spatial memory with both early [160] and late [161] administration of DA antagonists. For example, Kobori and Dash (2006) [161] demonstrated that a single administration of the DA D1 antagonist (SCH23390) at 14 days post-injury in rats improved WM. Tang et al. (1997) [160] showed an improvement in functional recovery with D2 receptor specific antagonists when given immediately post-injury and a synergistic effect when combined with D1 receptor antagonism in mice. Given that both haloperidol and risperidone have a higher affinity for the D2 receptors [162, 163], it may be that specific blockade of D2 receptors is the event most associated with negative outcomes when antagonized at later time-points.

Flanking the Problem

In addition to directly targeting DAgergic receptors, there are multiple therapeutics that indirectly affect the DAgergic pathway that have demonstrated significant neuroprotective properties [164]. The monoamine-oxidase B (MAO-B) inhibitor selegiline, which increases DA levels by inhibiting DA breakdown in the synaptic cleft, has been shown to protect against 1-methyl-4 phenylpyridinium (MPP⁺) toxicity in cell culture [165] and reduce DAergic cell loss in 1-methyl 4-phenyl 1, 2, 3, 6 tetrahydropyridine (MPTP) treated animals [166]. Selegiline has also been shown to reduce the levels of free radical generation by DA [167] and to reduce DBH immunoreactivity in the hippocampus [168]. Moreover, delayed (24 hours after injury) and chronic (days 1-7) administration of selegiline (l-deprenyl) following FPI has been reported to improve cognitive performance in a water maze task [168]. Lastly, selegiline has also been reported to reduce TBI-induced apathy in adults when given chronically [169].

Another MAO-B inhibitor, rasagiline, has been shown to protect against glutamatergic excitotoxicity [170]. Much like selegiline, rasagiline has shown efficacy in TBI. Specifically, when given to mice 5 min after a closed head injury rasagiline reduced edema and improved both motor function and spatial memory [171].

DA agonists, such as pramipexole and ropinirole, that possess a hydroxylated benzyl ring structure have proven antioxidant capacity [172] and demonstrated neuronal protection [173]. Both also have anti-apoptotic properties not linked to their actions on DA receptors [174] and neuroprotective benefits against oxidative stress that is partially mediated by DA receptor binding [175].

Fig. (1). Dopamine (DA) is a tightly regulated system that has potential negative consequences with increased or decreased dopaminergic tone. Several studies assessing DA report an increase immediately after TBI and a significant decrease at later stages. Therapeutic strategies should consider the implications of this bi-phasic response in DA systems after TBI.
Furthermore, pramipexole and ropinirole have been shown to have some neurotrophic properties leading to upregulation of brain derived and glial-cell derived growth factors [176]. In an experimental 28-day ischemia model, pramipexole given 1 hour post-injury reduced the post-ischemic loss of nigrostriatal DA neurons [177]. Clinically, there is evidence that pramipexole is beneficial after pediatric TBI when administered 1 month following injury in low-response patients [178].

CONCLUSION

The role that DA plays acutely following TBI is complex (Fig. 1). Whether the initial increase is neurotoxic or an attempt to restore functional circuitry damaged by the mechanical insult is unclear. However, LTD in DAergic signaling systems would suggest that the initial rise in DA tissue levels is a pathologic consequence of acute brain injury similar to the increased release of glutamate. A dramatic rise in DA within the CNS has multiple consequences including increased oxidative stress, induction of inflammatory signals, increased intracellular calcium, and signaling alterations caused by changes in intracellular signaling molecules. Taken together DAergic induction immediately post-TBI would appear to be detrimental. However, such an assertion is a dangerous over simplification of DA dysfunction. Much like glutamate, the blockade of DAergic signaling cascades can have serious detrimental side effects. What does appear to be clear is that acute administration of D1 receptor antagonists and D2 receptor agonists are beneficial after brain trauma. This is consistent with the role DA plays at the synapse. Many D2 receptors are located pre-synaptically and actually decrease DA release thus reducing the levels of potential oxidative stress [179, 180]. Furthermore DA targeted drugs, such as the MAO-B inhibitors, which act to increase DA levels, but reduce DAs metabolism, exert neuroprotective effects.

While significant research remains to be done on the role DA plays in acute brain injury, DAergic targeted therapies show real promise in addressing the concerns represented by acute brain injury and providing significant functional benefits.

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ABBREVIATIONS

6-OHDA = 6-Hydroxydopamine
AMH = Amantadine Hydrochloride
AMPA = α-amin0-3-hydroxyl-5-methyl-4-isoxazole-proprionate
AMPH = Amphetamine
ATP = Adenosine Tri-Phosphate
CCI = Controlled Cortical Impact
CREB = cAMP response element binding protein
DA = Dopamine
DARPP-32 = Dopamine, cAMP regulated phosphoprotein 32 kDa
DBH = Dopamine beta hydroxylase
ERK = Extracellular regulated kinase
FC = Frontal cortex
FPI = Fluid Percussion Injury
IL-1β = Interleukin 1β
MAO-B = Monoamine oxidase B
MPD = Methylphenidate
MPP+ = 1-methyl-4-phenylpyridinium
MPTP = 1-methyl 4-phenyl 1,2,3,6 tetrahydropyridine
NMDA = N-methyl-D-aspartate
PD = Parkinson’s Disease
PP-1 = Protein Phosphatase-1
STEP = Striatal Enriched Protein
TBI = Traumatic Brain Injury
TH = Tyrosine Hydroxylase

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