

Targeting Dopamine in Acute Traumatic Brain Injury

James W. Bales^{1,2,3,4}, Anthony E. Kline^{1,2,3,5,6}, Amy K. Wagner^{1,2,5} and C. Edward Dixon^{*,1,2,4,5}

¹Safar Center for Resuscitation Research, ²Center for Neuroscience, ³Center for the Neural Basis of Cognition, ⁴Neurological Surgery, ⁵Physical Medicine and Rehabilitation, ⁶Psychology, University of Pittsburgh, Pittsburgh, PA 15260, USA

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 DAergic innervating 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

*Address correspondence to this author at the Safar Center for Resuscitation Research, 201 Hill Bldg, 3434 Fifth Avenue, Pittsburgh, PA 15260, USA; Tel: (412) 383-1912; Fax: (412) 624-0943; E-mail: dixonec@upmc.edu

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-acutely 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-methyltransferase 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 prefrontal 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/quinone [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 Ca²⁺ 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 adenosine triphosphate (ATP) depletion [100]. In hypoxia-ischemia, there is increased expression and phosphorylation of the N-methyl-D-aspartic 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-1 β (IL-1 β) production [120, 121]. In TBI, blocking IL-1 β 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 improvement 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 enhanced 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 DAergic 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 DAergic 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 DAergic receptors, there are multiple therapeutics that indirectly affect the DAergic 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].

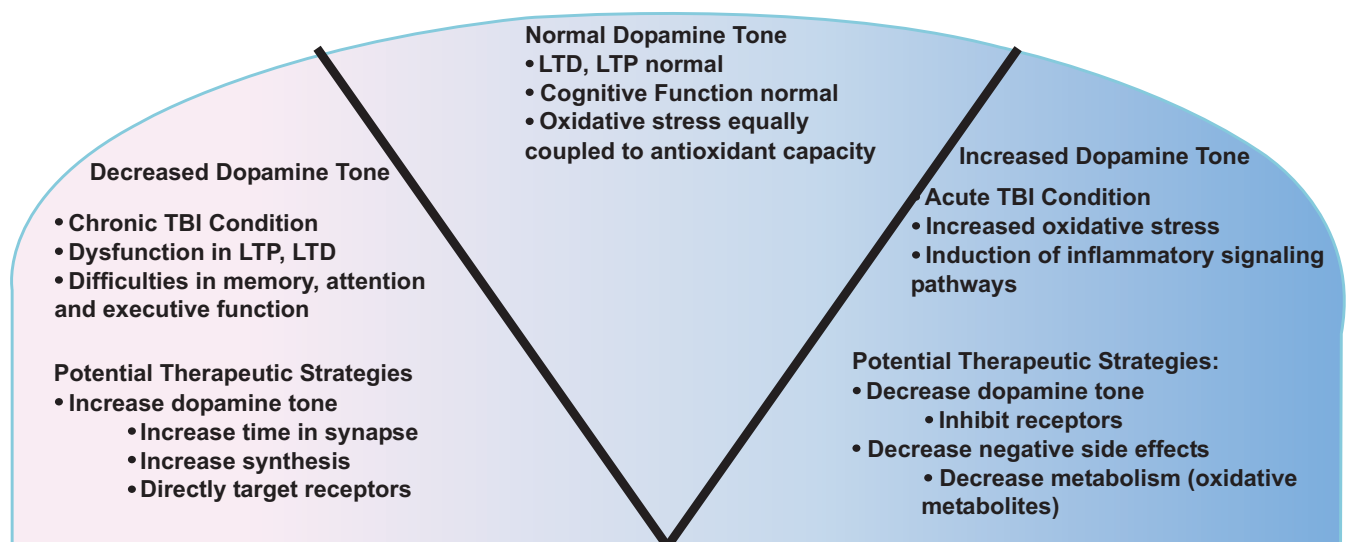


Fig. (1). Dopamine (DA) is a tightly regulated system that has potential negative consequences with increased or decreased dopaminergic tone. Several studies assessing DA report an increase immediately after TBI and a significant decrease at later stages. Therapeutic strategies should consider the implications 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 oversimplification 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.

ACKNOWLEDGEMENTS

This project is supported by: NIH/NINDS grant 5R01NS060672-02; NIH/NINDS grant 2P50NS030318; and the Veterans Affairs grant B6761R.

ABBREVIATIONS

6-OHDA	=	6-Hydroxydopamine
AMH	=	Amantadine Hydrochloride
AMPA	=	α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
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-1 β	=	Interleukin 1 β
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

REFERENCES

- [1] Kochanek, P.M. Ischemic and traumatic brain injury: pathobiology and cellular mechanisms. *Crit. Care Med.*, **1993**, 21(9 Suppl), S333-335.
- [2] Park, C.; Cho, I.H.; Kim, D.; Jo, E.K.; Choi, S.Y.; Oh, S.B.; Park, K.; Kim, J. S.; Lee, S.J. Toll-like receptor 2 contributes to glial cell activation and heme oxygenase-1 expression in traumatic brain injury. *Neurosci. Lett.*, **2008**, 431(2), 123-128.
- [3] Lighthall, J.W. Controlled cortical impact: a new experimental brain injury model. *J. Neurotrauma*, **1988**, 5(1), 1-15.
- [4] Dixon, C.E.; Clifton, G.L.; Lighthall, J.W.; Yaghai, A.A.; Hayes, R.L. A controlled cortical impact model of traumatic brain injury in the rat. *J. Neurosci. Methods*, **1991**, 39(3), 253-262.
- [5] Dixon, C.E.; Lyeth, B.G.; Povlishock, J.T.; Findling, R.L.; Hamm, R.J.; Marmarou, A.; Young, H.F.; Hayes, R.L. A fluid percussion model of experimental brain injury in the rat. *J. Neurosurg.*, **1987**, 67(1), 110-119.
- [6] Kline, A.E.; Massucci, J.L.; Zafonte, R.D.; Dixon, C.E.; DeFeo, J.R.; Rogers, E.H. Differential effects of single vs multiple administrations of haloperidol and risperidone on functional outcome after experimental brain trauma. *Crit. Care Med.*, **2007**, 35(3), 919-924.
- [7] Kline, A.E.; Wagner, A.K.; Westergom, B.P.; Malena, R.R.; Zafonte, R.D.; Olsen, A.S.; Sozda, C.N.; Luthra, P.; Panda, M.; Cheng, J.P.; Aslam, H.A. Acute treatment with the 5-HT(1A) receptor agonist 8-OH-DPAT and chronic environmental enrichment confer neurobehavioral benefit after experimental brain trauma. *Behav. Brain Res.*, **2007**, 177(2), 186-194.
- [8] Fox, G.B.; Fan, L.; LeVasseur, R.A.; Faden, A. Effect of traumatic brain injury on mouse spatial and nonspatial learning in the Barnes circular maze. *J. Neurotrauma*, **1998**, 15(12), 1037-1046.
- [9] Wagner, A.K.; Kline, A.E.; Sokoloski, J.; Zafonte, R.D.; Capulong, E.; Dixon, C.E. Intervention with environmental enrichment after experimental brain trauma enhances cognitive recovery in male but not female rats. *Neurosci. Lett.*, **2002**, 334(3), 165-168.
- [10] Wagner, A.K.; Willard, L.A.; Kline, A.E.; Wenger, M.K.; Bolinger, B.D.; Ren, D.; Zafonte, R.D.; Dixon, C.E. Evaluation of estrous cycle stage and gender on behavioral outcome after experimental traumatic brain injury. *Brain Res.*, **2004**, 998(1), 113-121.
- [11] Gualtieri, C.T. Pharmacotherapy and the neurobehavioural sequelae of traumatic brain injury. *Brain Inj.*, **1988**, 2(2), 101-129.
- [12] Toliás, C.M.; Bullock, M.R. Critical appraisal of neuroprotection trials in head injury: what have we learned? *NeuroRx*, **2004**, 1(1), 71-79.

- [13] Capone-Neto, A.; Rizoli, S.B. Linking the chain of survival: trauma as a traditional role model for multisystem trauma and brain injury. *Curr. Opin. Crit. Care*, **2009**, *15*(4), 290-294.
- [14] Ladanyi, S.; Elliott, D. Traumatic brain injury: an integrated clinical case presentation and literature review. Part I: assessment and initial management. *Aust. Crit. Care*, **2008**, *21*(2), 86-95.
- [15] Folkersma, H.; Boellaard, R.; Vandertop, W.P.; Kloet, R.W.; Lubberink, M.; Lammertsma, A.A.; van Berckel, B.N. Reference tissue models and blood-brain barrier disruption: lessons from (R)-[11C]PK11195 in traumatic brain injury. *J. Nucl. Med.*, **2009**, *50*(12), 1957-1959.
- [16] Whalen, M.J.; Carlos, T.M.; Kochanek, P.M.; Heineman, S. Blood-brain barrier permeability, neutrophil accumulation and vascular adhesion molecule expression after controlled cortical impact in rats: a preliminary study. *Acta Neurochir. Suppl.*, **1998**, *71*, 212-214.
- [17] Muir, K.W. Glutamate-based therapeutic approaches: clinical trials with NMDA antagonists. *Curr. Opin. Pharmacol.*, **2006**, *6*(1), 53-60.
- [18] Roberts, D.J.; Goralski, K.B.; Renton, K.W.; Julien, L.C.; Webber, A.M.; Sleno, L.; Volmer, D.A.; Hall, R.I. Effect of acute inflammatory brain injury on accumulation of morphine and morphine 3- and 6-glucuronide in the human brain. *Crit. Care Med.*, **2009**, *37*(10), 2767-2774.
- [19] Christoffersen, G.R.; Simonyi, A.; Schachtman, T.R.; Clausen, B.; Clement, D.; Bjerre, V.K.; Mark, L.T.; Reinholdt, M.; Schmith-Rasmussen, K.; Zink, L.V. mGlu5 antagonism impairs exploration and memory of spatial and non-spatial stimuli in rats. *Behav. Brain Res.*, **2008**, *191*(2), 235-245.
- [20] Gil-Sanz, C.; Delgado-Garcia, J.M.; Fairen, A.; Gruart, A. Involvement of the mGluR1 receptor in hippocampal synaptic plasticity and associative learning in behaving mice. *Cereb. Cortex*, **2008**, *18*(7), 1653-1663.
- [21] Parsons, C.G.; Stoffler, A.; Danysz, W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system--too little activation is bad, too much is even worse. *Neuropharmacology*, **2007**, *53*(6), 699-723.
- [22] Schotanus, S.M.; Chergui, K. Dopamine D1 receptors and group I metabotropic glutamate receptors contribute to the induction of long-term potentiation in the nucleus accumbens. *Neuropharmacology*, **2008**, *54*(5), 837-844.
- [23] Faden, A.I.; Demediuk, P.; Panter, S.S.; Vink, R. The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science*, **1989**, *244*(4906), 798-800.
- [24] Jennings, J. S.; Gerber, A. M.; Vallano, M. L. Pharmacological strategies for neuroprotection in traumatic brain injury. *Mini Rev. Med. Chem.*, **2008**, *8*(7), 689-701.
- [25] Bye, N.; Habgood, M.D.; Callaway, J.K.; Malakooti, N.; Potter, A.; Kossmann, T.; Morganti-Kossmann, M.C. Transient neuroprotection by minocycline following traumatic brain injury is associated with attenuated microglial activation but no changes in cell apoptosis or neutrophil infiltration. *Exp. Neurol.*, **2007**, *204*(1), 220-233.
- [26] Warden, D.L.; Gordon, B.; McAllister, T.W.; Silver, J.M.; Barth, J.T.; Bruns, J.; Drake, A.; Gentry, T.; Jagoda, A.; Katz, D.I.; Kraus, J.; Labbate, L.A.; Ryan, L.M.; Sparling, M.B.; Walters, B.; Whyte, J.; Zapata, A.; Zitnay, G. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *J. Neurotrauma*, **2006**, *23*(10), 1468-1501.
- [27] Whyte, J.; Hart, T.; Vaccaro, M.; Grieb-Neff, P.; Risser, A.; Polansky, M.; Coslett, H.B. Effects of methylphenidate on attention deficits after traumatic brain injury: a multidimensional, randomized, controlled trial. *Am. J. Phys. Med. Rehabil.*, **2004**, *83*(6), 401-420.
- [28] Hicks, R.R.; Smith, D.H.; Lowenstein, D.H.; Saint Marie, R.; McIntosh, T.K. Mild experimental brain injury in the rat induces cognitive deficits associated with regional neuronal loss in the hippocampus. *J. Neurotrauma*, **1993**, *10*(4), 405-414.
- [29] Sanders, M.J.; Dietrich, W.D.; Green, E.J. Behavioral, electrophysiological, and histopathological consequences of mild fluid-percussion injury in the rat. *Brain Res.*, **2001**, *904*(1), 141-144.
- [30] Lighthall, J.W.; Dixon, C.E.; Anderson, T.E. Experimental models of brain injury. *J. Neurotrauma*, **1989**, *6*(2), 83-97.
- [31] Dietrich, W.D.; Alonso, O.; Halley, M. Early microvascular and neuronal consequences of traumatic brain injury: a light and electron microscopic study in rats. *J. Neurotrauma*, **1994**, *11*(3), 289-301.
- [32] Baddeley, A.; Logie, R.; Bressi, S.; Della Sala, S.; Spinnler, H. Dementia and working memory. *Q. J. Exp. Psychol. A.*, **1986**, *38*(4), 603-618.
- [33] Buckley, M.J. The role of the perirhinal cortex and hippocampus in learning, memory, and perception. *Q. J. Exp. Psychol. B.*, **2005**, *58*(3-4), 246-268.
- [34] Cohen, J.D.; Servan-Schreiber, D. Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. *Psychol. Rev.*, **1992**, *99*(1), 45-77.
- [35] Izquierdo, I.; Quillfeldt, J.A.; Zanatta, M.S.; Quevedo, J.; Schaeffer, E.; Schmitz, P.K.; Medina, J.H. Sequential role of hippocampus and amygdala, entorhinal cortex and parietal cortex in formation and retrieval of memory for inhibitory avoidance in rats. *Eur. J. Neurosci.*, **1997**, *9*(4), 786-793.
- [36] Raz, A. Anatomy of attentional networks. *Anat. Rec. B. New Anat.*, **2004**, *281*(1), 21-36.
- [37] Binder, L.M. Neurobehavioral recovery after mild head injury. *J. Neurosurg.*, **1987**, *67*(5), 785-787.
- [38] Levin, H. S. Memory deficit after closed head injury. *J. Clin. Exp. Neuropsychol.*, **1990**, *12*(1), 129-53.
- [39] Levin, H.S.; Gary, H.E. Jr.; Eisenberg, H.M.; Ruff, R.M.; Barth, J.T.; Kreutzer, J.; High, W.M. Jr.; Portman, S.; Foulkes, M.A.; Jane, J.A.; et al. Neurobehavioral outcome 1 year after severe head injury. Experience of the Traumatic Coma Data Bank. *J. Neurosurg.*, **1990**, *73*(5), 699-709.
- [40] McDonald, B.C.; Flashman, L.A.; Saykin, A.J. Executive dysfunction following traumatic brain injury: neural substrates and treatment strategies. *NeuroRehabilitation*, **2002**, *17*(4), 333-344.
- [41] McDowell, S.; Whyte, J.; D'Esposito, M. Working memory impairments in traumatic brain injury: evidence from a dual-task paradigm. *Neuropsychologia*, **1997**, *35*(10), 1341-1353.
- [42] Millis, S.R.; Rosenthal, M.; Novack, T.A.; Sherer, M.; Nick, T.G.; Kreutzer, J.S.; High, W.M. Jr.; Ricker, J.H. Long-term neuropsychological outcome after traumatic brain injury. *J. Head Trauma Rehabil.*, **2001**, *16*(4), 343-355.
- [43] Centonze, D.; Gubellini, P.; Picconi, B.; Calabresi, P.; Giacomini, P.; Bernardi, G. Unilateral dopamine denervation blocks corticostriatal LTP. *J. Neurophysiol.*, **1999**, *82*(6), 3575-3579.
- [44] Chen, L.; Bohanick, J.D.; Nishihara, M.; Seamans, J.K.; Yang, C.R. Dopamine D1/5 receptor-mediated long-term potentiation of intrinsic excitability in rat prefrontal cortical neurons: Ca²⁺-dependent intracellular signaling. *J. Neurophysiol.*, **2007**, *97*(3), 2448-2464.
- [45] Granado, N.; Ortiz, O.; Suarez, L.M.; Martin, E.D.; Cena, V.; Solis, J.M.; Moratalla, R. D1 but not D5 dopamine receptors are critical for LTP, spatial learning, and LTP-Induced arc and zif268 expression in the hippocampus. *Cereb. Cortex*, **2008**, *18*(1), 1-12.
- [46] O'Carroll, C. M.; Martin, S. J.; Sandin, J.; Frenguelli, B.; Morris, R. G. Dopaminergic modulation of the persistence of one-trial hippocampus-dependent memory. *Learn. Mem.*, **2006**, *13*(6), 760-769.
- [47] Bramlett, H.M.; Dietrich, W.D. Quantitative structural changes in white and gray matter 1 year following traumatic brain injury in rats. *Acta Neuropathol.*, **2002**, *103*(6), 607-614.
- [48] Meythaler, J.M.; Peduzzi, J.D.; Eleftheriou, E.; Novack, T.A. Current concepts: diffuse axonal injury-associated traumatic brain injury. *Arch. Phys. Med. Rehabil.*, **2001**, *82*(10), 1461-1471.
- [49] Reeves, T.M.; Phillips, L.L.; Lee, N.N.; Povlishock, J.T. Preferential neuroprotective effect of tacrolimus (FK506) on unmyelinated axons following traumatic brain injury. *Brain Res.*, **2007**, *1154*, 225-236.
- [50] Smith, D.H.; Meaney, D.F.; Shull, W.H. Diffuse axonal injury in head trauma. *J. Head Trauma Rehabil.*, **2003**, *18*(4), 307-316.
- [51] Blanchard, V.; Chritin, M.; Vyas, S.; Savasta, M.; Feuerstein, C.; Agid, Y.; Javoy-Agid, F.; Raisman-Vozari, R. Long-term induction of tyrosine hydroxylase expression: compensatory response to partial degeneration of the dopaminergic nigrostriatal system in the rat brain. *J. Neurochem.*, **1995**, *64*(4), 1669-1679.
- [52] Mura, A.; Feldon, J. Spatial learning in rats is impaired after degeneration of the nigrostriatal dopaminergic system. *Mov. Disord.*, **2003**, *18*(8), 860-871.
- [53] Onn, S.P.; Berger, T.W.; Stricker, E.M.; Zigmond, M.J. Effects of intraventricular 6-hydroxydopamine on the dopaminergic

- innervation of striatum: histochemical and neurochemical analysis. *Brain Res.*, **1986**, 376(1), 8-19.
- [54] Butefisch, C.M.; Davis, B.C.; Sawaki, L.; Waldvogel, D.; Classen, J.; Kopylev, L.; Cohen, L.G. Modulation of use-dependent plasticity by d-amphetamine. *Ann. Neurol.*, **2002**, 51(1), 59-68.
- [55] Tanaka, K.; Ogawa, N.; Asanuma, M. Molecular basis of 6-hydroxydopamine-induced caspase activations due to increases in oxidative stress in the mouse striatum. *Neurosci. Lett.*, **2006**, 410(2), 85-89.
- [56] Viggiano, D.; Vallone, D.; Ruocco, L. A.; Sadile, A.G. Behavioural, pharmacological, morpho-functional molecular studies reveal a hyperfunctioning mesocortical dopamine system in an animal model of attention deficit and hyperactivity disorder. *Neurosci. Biobehav. Rev.*, **2003**, 27(7), 683-689.
- [57] Griesbach, G.S.; Hovda, D.A.; Gomez-Pinilla, F.; Sutton, R.L. Voluntary exercise or amphetamine treatment, but not the combination, increases hippocampal brain-derived neurotrophic factor and synapsin I following cortical contusion injury in rats. *Neuroscience*, **2008**, 154(2), 530-540.
- [58] Haracz, J.L.; Tschanz, J.T.; Wang, Z.; Griffith, K.E.; Rebec, G.V. Amphetamine effects on striatal neurons: implications for models of dopamine function. *Neurosci. Biobehav. Rev.*, **1998**, 22(5), 613-622.
- [59] Yan, H. Q.; Kline, A.E.; Ma, X.; Hooghe-Peters, E.L.; Marion, D.W.; Dixon, C.E. Tyrosine hydroxylase, but not dopamine beta-hydroxylase, is increased in rat frontal cortex after traumatic brain injury. *Neuroreport*, **2001**, 12(11), 2323-2327.
- [60] Kobori, N.; Clifton, G.L.; Dash, P.K. Enhanced catecholamine synthesis in the prefrontal cortex after traumatic brain injury: implications for prefrontal dysfunction. *J. Neurotrauma*, **2006**, 23(7), 1094-1102.
- [61] Yan, H. Q.; Ma, X.; Chen, X.; Li, Y.; Shao, L.; Dixon, C.E. Delayed increase of tyrosine hydroxylase expression in rat nigrostriatal system after traumatic brain injury. *Brain Res.*, **2007**, 1134(1), 171-179.
- [62] Huger, F.; Patrick, G. Effect of concussive head injury on central catecholamine levels and synthesis rates in rat brain regions. *J. Neurochem.*, **1979**, 33(1), 89-95.
- [63] Dunn-Meynell, A.; Pan, S.; Levin, B.E. Focal traumatic brain injury causes widespread reductions in rat brain norepinephrine turnover from 6 to 24 h. *Brain Res.*, **1994**, 660(1), 88-95.
- [64] McIntosh, T.K.; Yu, T.; Gennarelli, T.A. Alterations in regional brain catecholamine concentrations after experimental brain injury in the rat. *J. Neurochem.*, **1994**, 63(4), 1426-1433.
- [65] Massucci, J.L.; Kline, A.E.; Ma, X.; Zafonte, R.D.; Dixon, C.E. Time dependent alterations in dopamine tissue levels and metabolism after experimental traumatic brain injury in rats. *Neurosci. Lett.*, **2004**, 372(1-2), 127-131.
- [66] Redell, J.B.; Dash, P.K. Traumatic brain injury stimulates hippocampal catechol-O-methyl transferase expression in microglia. *Neurosci. Lett.*, **2007**, 413(1), 36-41.
- [67] Henry, J.M.; Talukder, N.K.; Lee, A.B. Jr.; Walker, M.L. Cerebral trauma-induced changes in corpus striatal dopamine receptor subtypes. *J. Invest. Surg.*, **1997**, 10(5), 281-286.
- [68] Alexander, G.E.; Crutcher, M.D. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci.*, **1990**, 13(7), 266-271.
- [69] Graybiel, A.M. Neurotransmitters and neuromodulators in the basal ganglia. *Trends Neurosci.*, **1990**, 13(7), 244-254.
- [70] Meredith, G.E.; Wouterlood, F.G.; Pattiselanno, A. Hippocampal fibers make synaptic contacts with glutamate decarboxylase-immunoreactive neurons in the rat nucleus accumbens. *Brain Res.*, **1990**, 513(2), 329-334.
- [71] Calabresi, P.; Gubellini, P.; Centonze, D.; Picconi, B.; Bernardi, G.; Chergui, K.; Svenningsson, P.; Fienberg, A.A.; Greengard, P. Dopamine and cAMP-regulated phosphoprotein 32 kDa controls both striatal long-term depression and long-term potentiation, opposing forms of synaptic plasticity. *J. Neurosci.*, **2000**, 20(22), 8443-8451.
- [72] Li, S.; Cullen, W.K.; Anwyl, R.; Rowan, M.J. Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nat. Neurosci.*, **2003**, 6(5), 526-531.
- [73] Lemon, N.; Manahan-Vaughan, D. Dopamine D1/D5 receptors gate the acquisition of novel information through hippocampal long-term potentiation and long-term depression. *J. Neurosci.*, **2006**, 26(29), 7723-7729.
- [74] Williams, G.V.; Castner, S.A. Under the curve: critical issues for elucidating D1 receptor function in working memory. *Neuroscience*, **2006**, 139(1), 263-276.
- [75] Goldberg, T.E.; Bigelow, L.B.; Weinberger, D.R.; Daniel, D.G.; Kleinman, J.E. Cognitive and behavioral effects of the coadministration of dextroamphetamine and haloperidol in schizophrenia. *Am. J. Psychiatry*, **1991**, 148(1), 78-84.
- [76] Schneider, J.S.; Roeltgen, D.P. Delayed matching-to-sample, object retrieval, and discrimination reversal deficits in chronic low dose MPTP-treated monkeys. *Brain Res.*, **1993**, 615(2), 351-354.
- [77] Arnsten, A.F.; Goldman-Rakic, P.S. Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. *Arch. Gen. Psychiatry*, **1998**, 55(4), 362-368.
- [78] Morrow, B.A.; Roth, R.H.; Elsworth, J.D. TMT, a predator odor, elevates mesoprefrontal dopamine metabolic activity and disrupts short-term working memory in the rat. *Brain Res. Bull.*, **2000**, 52(6), 519-523.
- [79] Olney, J.W.; Zorumski, C.F.; Stewart, G.R.; Price, M.T.; Wang, G.J.; Labruyere, J. Excitotoxicity of L-dopa and 6-OH-dopa: implications for Parkinson's and Huntington's diseases. *Exp. Neurol.*, **1990**, 108(3), 269-272.
- [80] Hastings, T.G. Enzymatic oxidation of dopamine: the role of prostaglandin H synthase. *J. Neurochem.*, **1995**, 64(2), 919-924.
- [81] Sinet, P.M.; Heikkila, R.E.; Cohen, G. Hydrogen peroxide production by rat brain *in vivo*. *J. Neurochem.*, **1980**, 34(6), 1421-1428.
- [82] Brunmark, A.; Cadenas, E. Oxidation of quinines by H₂O₂: formation of epoxy- and hydroxyquinone adducts and electronically excited states. *Basic Life Sci.*, **1988**, 49, 81-86.
- [83] Beal, M.F. Experimental models of Parkinson's disease. *Nat. Rev. Neurosci.*, **2001**, 2(5), 325-334.
- [84] Blum, D.; Torch, S.; Lambeng, N.; Nissou, M.; Benabid, A.L.; Sadoul, R.; Verna, J.M. Molecular pathways involved in the neurotoxicity of 6-OHDA, dopamine and MPTP: contribution to the apoptotic theory in Parkinson's disease. *Prog. Neurobiol.*, **2001**, 65(2), 135-172.
- [85] Azdad, K.; Gall, D.; Woods, A.S.; Ledent, C.; Ferre, S.; Schiffmann, S.N. Dopamine D2 and adenosine A2A receptors regulate NMDA-mediated excitation in accumbens neurons through A2A-D2 receptor heteromerization. *Neuropsychopharmacology*, **2009**, 34(4), 972-986.
- [86] Hernandez-Lopez, S.; Tkatch, T.; Perez-Garci, E.; Galarraga, E.; Bargas, J.; Hamm, H.; Surmeier, D.J. D2 dopamine receptors in striatal medium spiny neurons reduce L-type Ca²⁺ currents and excitability via a novel PLC[β]-IP3-calcineurin-signaling cascade. *J. Neurosci.*, **2000**, 20(24), 8987-8995.
- [87] So, C.H.; Verma, V.; Aljaniam, M.; Cheng, R.; Rashid, A.J.; O'Dowd, B.F.; George, S.R. Calcium signaling by dopamine D5 receptor and D5-D2 receptor hetero-oligomers occurs by a mechanism distinct from that for dopamine D1-D2 receptor hetero-oligomers. *Mol. Pharmacol.*, **2009**, 75(4), 843-854.
- [88] Palmer, A.M.; Marion, D.W.; Botscheller, M.L.; Swedlow, P.E.; Styren, S.D.; DeKosky, S.T. Traumatic brain injury-induced excitotoxicity assessed in a controlled cortical impact model. *J. Neurochem.*, **1993**, 61(6), 2015-2024.
- [89] Rao, V.L.; Dogan, A.; Bowen, K.K.; Dempsey, R.J. Traumatic injury to rat brain upregulates neuronal nitric oxide synthase expression and L-[3H]nitroarginine binding. *J. Neurotrauma*, **1999**, 16(10), 865-877.
- [90] Chapman, A.G.; Durmuller, N.; Lees, G.J.; Meldrum, B.S. Excitotoxicity of NMDA and kainic acid is modulated by nigrostriatal dopaminergic fibres. *Neurosci. Lett.*, **1989**, 107(1-3), 256-260.
- [91] Filloux, F.; Wamsley, J.K. Dopaminergic modulation of excitotoxicity in rat striatum: evidence from nigrostriatal lesions. *Synapse*, **1991**, 8(4), 281-288.
- [92] Wagner, A.K.; Sokoloski, J.E.; Ren, D.; Chen, X.; Khan, A.S.; Zafonte, R.D.; Michael, A.C.; Dixon, C.E. Controlled cortical impact injury affects dopaminergic transmission in the rat striatum. *J. Neurochem.*, **2005**, 95(2), 457-465.
- [93] Globus, M.Y.; Busto, R.; Dietrich, W.D.; Martinez, E.; Valdes, I.; Ginsberg, M.D. Effect of ischemia on the *in vivo* release of striatal dopamine, glutamate, and γ -aminobutyric acid studied by intracerebral microdialysis. *J. Neurochem.*, **1988**, 51, 1455-1464.

- [94] Globus, M.Y.; Ginsberg, M.D.; Dietrich, W.D.; Busto, R.; Scheinberg, P. Substantia nigra lesion protects against ischemic damage in the striatum. *Neurosci. Lett.*, **1987**, *80*, 251-256.
- [95] Fineman, I.; Hovda, D.A.; Smith, M.; Yoshino, A.; Becker, D.P. Concussive brain injury is associated with a prolonged accumulation of calcium: a ⁴⁵Ca autoradiographic study. *Brain Res.*, **1993**, *624*(1-2), 94-102.
- [96] Shapira, Y.; Yadid, G.; Cotev, S.; Shohami, E. Accumulation of calcium in the brain following head trauma. *Neurol. Res.*, **1989**, *11*(3), 169-172.
- [97] Osteen, C.L.; Giza, C.C.; Hovda, D.A. Injury-induced alterations in N-methyl-D-aspartate receptor subunit composition contribute to prolonged ⁴⁵calcium accumulation following lateral fluid percussion. *Neuroscience*, **2004**, *128*(2), 305-322.
- [98] Ross, S.T.; Soltesz, I. Selective depolarization of interneurons in the early posttraumatic dentate gyrus: involvement of the Na(+)/K(+)-ATPase. *J. Neurophysiol.*, **2000**, *83*(5), 2916-2930.
- [99] Dixon, C.E.; Bao, J.; Johnson, K.M.; Yang, K.; Whitson, J.; Clifton, G.L.; Hayes, R.L. Basal and scopolamine-evoked release of hippocampal acetylcholine following traumatic brain injury in rats. *Neurosci. Lett.*, **1995**, *198*(2), 111-114.
- [100] Yoshino, A.; Hovda, D.A.; Kawamata, T.; Katayama, Y.; Becker, D.P. Dynamic changes in local cerebral glucose utilization following cerebral concussion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Res.*, **1991**, *561*(1), 106-119.
- [101] Yang, Z.; Torbey, M.; Li, X.; Bernardy, J.; Golden, W.C.; Martin, L.J.; Koehler, R.C. Dopamine receptor modulation of hypoxic-ischemic neuronal injury in striatum of newborn piglets. *J. Cereb. Blood Flow Metab.*, **2007**, *27*, 1339-1351.
- [102] Kumar, A.; Zou, L.; Yuan, X.; Long, Y.; Yang, K. N-methyl-D-aspartate receptors: transient loss of NR1/NR2A/NR2B subunits after traumatic brain injury in a rodent model. *J. Neurosci. Res.*, **2002**, *67*(6), 781-786.
- [103] Nishi, A.; Bibb, J.A.; Matsuyama, S.; Hamada, M.; Higashi, H.; Nairn, A.C.; Greengard, P. Regulation of DARPP-32 dephosphorylation at PKA- and Cdk5-sites by NMDA and AMPA receptors: distinct roles of calcineurin and protein phosphatase-2A. *J. Neurochem.*, **2002**, *81*(4), 832-841.
- [104] Greengard, P.; Allen, P.B.; Nairn, A.C. Beyond the dopamine receptor: the DARPP-32/protein phosphatase-1 cascade. *Neuron*, **1999**, *23*(3), 435-447.
- [105] Paul, S.; Nairn, A.C.; Wang, P.; Lombroso, P.J. NMDA-mediated activation of the tyrosine phosphatase STEP regulates the duration of ERK signaling. *Nat. Neurosci.*, **2003**, *6*(1), 34-42.
- [106] Snyder, G.L.; Fienberg, A.A.; Haganir, R.L.; Greengard, P.A. Dopamine/D1 receptor/protein kinase A/dopamine- and cAMP-regulated phosphoprotein (Mr 32 kDa)/protein phosphatase-1 pathway regulates dephosphorylation of the NMDA receptor. *J. Neurosci.*, **1998**, *18*(24), 10297-10303.
- [107] Fienberg, A.A.; Hiroi, N.; Mermelstein, P.G.; Song, W.; Snyder, G. L.; Nishi, A.; Cheramy, A.; O'Callaghan, J.P.; Miller, D.B.; Cole, D.G.; Corbett, R.; Haile, C.N.; Cooper, D.C.; Onn, S.P.; Grace, A.A.; Ouimet, C.C.; White, F.J.; Hyman, S.E.; Surmeier, D.J.; Girault, J.; Nestler, E.J.; Greengard, P. DARPP-32: regulator of the efficacy of dopaminergic neurotransmission. *Science*, **1998**, *281*(5378), 838-842.
- [108] Flores-Hernandez, J.; Cepeda, C.; Hernandez-Echeagaray, E.; Calvert, C.R.; Jokel, E.S.; Fienberg, A.A.; Greengard, P.; Levine, M.S. Dopamine enhancement of NMDA currents in dissociated medium-sized striatal neurons: role of D1 receptors and DARPP-32. *J. Neurophysiol.*, **2002**, *88*(6), 3010-3020.
- [109] Canals, M.; Marcellino, D.; Fanelli, F.; Ciruela, F.; de Benedetti, P.; Goldberg, S.R.; Neve, K.; Fuxe, K.; Agnati, L.F.; Woods, A.S.; Ferre, S.; Lluis, C.; Bouvier, M.; Franco, R. Adenosine A2A-dopamine D2 receptor-receptor heteromerization: qualitative and quantitative assessment by fluorescence and bioluminescence energy transfer. *J. Biol. Chem.*, **2003**, *278*(47), 46741-46749.
- [110] Fuxe, K.; Ferre, S.; Canals, M.; Torvinen, M.; Terasmaa, A.; Marcellino, D.; Goldberg, S.R.; Staines, W.; Jacobsen, K.X.; Lluis, C.; Woods, A.S.; Agnati, L.F.; Franco, R. Adenosine A2A and dopamine D2 heteromeric receptor complexes and their function. *J. Mol. Neurosci.*, **2005**, *26*(2-3), 209-220.
- [111] Kurz, J.E.; Parsons, J.T.; Rana, A.; Gibson, C.J.; Hamm, R.J.; Churn, S.B. A significant increase in both basal and maximal calcineurin activity following fluid percussion injury in the rat. *J. Neurotrauma*, **2005**, *22*(4), 476-90.
- [112] Bales, J.W.; Ma, X.; Yan, H.Q.; Jenkins, L.W.; Dixon, C.E. Expression of protein phosphatase 2B (calcineurin) subunit A isoforms in rat hippocampus following a traumatic brain injury. *J. Neurotrauma*, **2010**, *27*(10), 109-120.
- [113] Kurz, J.E.; Hamm, R.J.; Singleton, R.H.; Povlishock, J.T.; Churn, S.B. A persistent change in subcellular distribution of calcineurin following fluid percussion injury in the rat. *Brain Res.*, **2005**, *1048*(1-2), 153-160.
- [114] Clausen, F.; Hanell, A.; Bjork, M.; Hillered, L.; Mir, A.K.; Gram, H.; Marklund, N. Neutralization of interleukin-1beta modifies the inflammatory response and improves histological and cognitive outcome following traumatic brain injury in mice. *Eur. J. Neurosci.*, **2009**, *30*(3), 385-396.
- [115] Kelso, M.L.; Scheff, S.W.; Pauly, J.R.; Loftin, C.D. Effects of genetic deficiency of cyclooxygenase-1 or cyclooxygenase-2 on functional and histological outcomes following traumatic brain injury in mice. *BMC Neurosci.*, **2009**, *10*, 108.
- [116] Khan, M.; Im, Y.B.; Shunmugavel, A.; Gilg, A.G.; Dhindsa, R.K.; Singh, A.K.; Singh, I. Administration of S-nitrosoglutathione after traumatic brain injury protects the neurovascular unit and reduces secondary injury in a rat model of controlled cortical impact. *J. Neuroinflammation*, **2009**, *6*, 32.
- [117] Ekdahl, C.T.; Kokaia, Z.; Lindvall, O. Brain inflammation and adult neurogenesis: the dual role of microglia. *Neuroscience*, **2009**, *158*(3), 1021-1029.
- [118] Kriz, J. Inflammation in ischemic brain injury: timing is important. *Crit. Rev. Neurobiol.*, **2006**, *18*(1-2), 145-157.
- [119] Farber, K.; Kettenmann, H. Physiology of microglial cells. *Brain Res. Rev.*, **2005**, *48*, 133-143.
- [120] Barnum, C.J.; Eskow, K.L.; Dupre, K.; Blandino Jr. P.; Deak, T.; Bishop, C. Exogenous corticosterone reduces L-dopa induced dyskinesia in the hemi-parkinsonian rat: role for interleukin-1β. *Neuroscience*, **2008**, *156*, 30-41.
- [121] Jiang, B.; Xu, S.; Hou, X.; Pimentel, D.; Brecher, P.; Cohen, R. Temporal control of NF-κB activation by ERK differentially regulates interleukin-1beta-induced gene expression. *J. Biol. Chem.*, **2004**, *279*(2), 1323-1329.
- [122] Kim, Y.S.; Joh, T.H. Microglia, major player in the brain inflammation: their roles in the pathogenesis of Parkinson's disease. *Exp. Mol. Med.*, **2006**, *38*(4), 333-347.
- [123] Teismann, P.; Schulz, J.B. Cellular pathology of Parkinson's disease: astrocytes, microglia, and inflammation. *Cell Tissue Res.*, **2004**, *318*(1), 149-161.
- [124] Mastroeni, D.; Grover, A.; Leonard, B.; Joyce, J.N.; Coleman, P.D.; Kozik, B.; Bellingier, D.L.; Rogers, J. Microglia responses to dopamine in a cell culture model of Parkinson's disease. *Neurobiol. Aging*, **2009**, *30*(11), 1805-1817.
- [125] Brustolim, D.; Ribeiro-dos-Santos, R.; Kast, R.E.; Altshuler, E.L.; Soares, M.B. A new chapter opens in anti-inflammatory treatments: the antidepressant bupropion lowers production of tumor necrosis factor-alpha and interferon-gamma in mice. *Int. Immunopharmacol.*, **2006**, *6*(6), 903-907.
- [126] Gualtieri, C.T.; Evans, R.W. Stimulant treatment for the neurobehavioural sequelae of traumatic brain injury. *Brain Inj.*, **1988**, *2*(4), 273-290.
- [127] Kraus, M.F.; Smith, G.S.; Butters, M.; Donnell, A.J.; Dixon, E.; Yilong, C.; Marion, D. Effects of the dopaminergic agent and NMDA receptor antagonist amantadine on cognitive function, cerebral glucose metabolism and D2 receptor availability in chronic traumatic brain injury: a study using positron emission tomography (PET). *Brain Inj.*, **2005**, *19*(7), 471-479.
- [128] McDowell, S.; Whyte, J.; D'Esposito, M. Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. *Brain*, **1998**, *121*(Pt 6), 1155-1164.
- [129] Kaelin, D. L.; Cifu, D.X.; Matthies, B. Methylphenidate effect on attention deficit in the acutely brain-injured adult. *Arch. Phys. Med. Rehabil.*, **1996**, *77*(1), 6-9.
- [130] Von Voigtlander, P.F.; Moore, K.E. Dopamine: release from the brain *in vivo* by amantadine. *Science*, **1971**, *174*(7), 408-410.
- [131] Gianutsos, G.; Chute, S.; Dunn, J.P. Pharmacological changes in dopaminergic systems induced by long-term administration of amantadine. *Eur. J. Pharmacol.*, **1985**, *110*(3), 357-361.
- [132] Chandler, M.C.; Barnhill, J.L.; Gualtieri, C.T. Amantadine for the agitated head-injury patient. *Brain Inj.*, **1988**, *2*(4), 309-311.

- [133] Saniova, B.; Drobny, M.; Kneslova, L.; Minarik, M. The outcome of patients with severe head injuries treated with amantadine sulphate. *J. Neural. Transm.*, **2004**, *111*, 511-514.
- [134] Saniova, B.; Drobny, M.; Lehotsky, J.; Sulaj, M.; Schudinova, J. Biochemical and clinical improvement of cytotoxic state by amantadine sulphate. *Cell Mol. Neurobiol.*, **2006**, *26*, 1475-1482.
- [135] Volz, T.J. Neuropharmacological mechanisms underlying the neuroprotective effects of methylphenidate. *Curr. Neuropharmacol.*, **2008**, *6* (4), 379-385.
- [136] Kline, A.E.; Chen, M.J.; Tso-Olivas, D.Y.; Feeney, D.M. Methylphenidate treatment following ablation-induced hemiplegia in rat: experience during drug action alters effects on recovery of function. *Pharmacol. Biochem. Behav.*, **1994**, *48*(3), 773-779.
- [137] Kline, A.E.; Yan, H.Q.; Bao, J.; Marion, D.W.; Dixon, C.E. Chronic methylphenidate treatment enhances water maze performance following traumatic brain injury in rats. *Neurosci. Lett.*, **2000**, *280*(3), 163-166.
- [138] Wagner, A.K.; Drowencki, L.L.; Chen, X.; Santos, F.R.; Khan, A.S.; Harun, R.; Torres, G.E.; Michael, A.C.; Dixon, C.E. Chronic methylphenidate treatment enhances striatal dopamine neurotransmission after experimental traumatic brain injury. *J. Neurochem.*, **2009**, *108*(4), 986-997.
- [139] Dhillon, H.S.; Dose, J.M.; Prasad, R.M. Amphetamine administration improves neurochemical outcome of lateral fluid percussion brain injury in the rat. *Brain Res.*, **1998**, *804*(2), 231-237.
- [140] Feeney, D.M.; Gonzales, A.; Law, W.A. Amphetamine restores locomotor function after motor cortex injury in the rat. *Proc. West. Pharmacol. Soc.*, **1981**, *24*, 15-17.
- [141] Hovda, D.A.; Sutton, R.L.; Feeney, D.M. Amphetamine-induced recovery of visual cliff performance after bilateral visual cortex ablation in cats: measurements of depth perception thresholds. *Behav. Neurosci.*, **1989**, *103*(3), 574-584.
- [142] M'Harzi, M.; Willig, F.; Costa, J.C.; Delacour, J. d-Amphetamine enhances memory performance in rats with damage to the fimbria. *Physiol. Behav.*, **1988**, *42*(6), 575-579.
- [143] Chudasama, Y.; Nathwani, F.; Robbins, T.W. D-Amphetamine remediates attentional performance in rats with dorsal prefrontal lesions. *Behav. Brain Res.*, **2005**, *158*(1), 97-107.
- [144] Queen, S.A.; Chen, M.J.; Feeney, D.M. d-Amphetamine attenuates decreased cerebral glucose utilization after unilateral sensorimotor cortex contusion in rats. *Brain Res.*, **1997**, *777*(1-2), 42-50.
- [145] Goldstein, L.B. Neuropharmacology of TBI-induced plasticity. *Brain Inj.*, **2003**, *17*(8), 685-694.
- [146] Ramic, M.; Emerick, A.J.; Bollnow, M.R.; O'Brien, T.E.; Tsai, S. Y.; Kartje, G.L. Axonal plasticity is associated with motor recovery following amphetamine treatment combined with rehabilitation after brain injury in the adult rat. *Brain Res.*, **2006**, *1111*(1), 176-186.
- [147] Fleckenstein, A.E.; Volz, T.J.; Riddle, E.L.; Gibb, J.W.; Hanson, G.R. New insights into the mechanism of action of amphetamines. *Annu. Rev. Pharmacol. Toxicol.*, **2007**, *47*, 681-698.
- [148] Boyeson, M.G.; Feeney, D.M. Intraventricular norepinephrine facilitates motor recovery following sensorimotor cortex injury. *Pharmacol. Biochem. Behav.*, **1990**, *35*(3), 497-501.
- [149] Feeney, D.M.; Gonzalez, A.; Law, W.A. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science*, **1982**, *217*(4562), 855-857.
- [150] Hovda, D.A.; Feeney, D.M. Haloperidol blocks amphetamine induced recovery of binocular depth perception after bilateral visual cortex ablation in cat. *Proc. West. Pharmacol. Soc.*, **1985**, *28*, 209-211.
- [151] Dixon, C.E.; Kraus, M.F.; Kline, A.E.; Ma, X.; Yan, H.Q.; Griffith, R.G.; Wolfson, B.M.; Marion, D.W. Amantadine improves water maze performance without affecting motor behavior following traumatic brain injury in rats. *Restor. Neurol. Neurosci.*, **1999**, *14*(4), 285-294.
- [152] Kihara, T.; Shimohama, S.; Sawada, H.; Honda, K.; Nakamizo, T.; Kanki, R.; Yamashita, H.; Akaike, A. Protective effect of dopamine D2 agonists in cortical neurons via the phosphatidylinositol 3 kinase cascade. *J. Neurosci. Res.*, **2002**, *70*(3), 274-282.
- [153] Kline, A.E.; Massucci, J.L.; Marion, D.W.; Dixon, C.E. Attenuation of working memory and spatial acquisition deficits after a delayed and chronic bromocriptine treatment regimen in rats subjected to traumatic brain injury by controlled cortical impact. *J. Neurotrauma*, **2002**, *19*(4), 415-425.
- [154] Kline, A.E.; Massucci, J.L.; Ma, X.; Zafonte, R.D.; Dixon, C.E. Bromocriptine reduces lipid peroxidation and enhances spatial learning and hippocampal neuron survival in a rodent model of focal brain trauma. *J. Neurotrauma*, **2004**, *21*(12), 1712-1722.
- [155] Armentero, M.T.; Fancellu, R.; Nappi, G.; Blandini, F. Dopamine receptor agonists mediate neuroprotection in malonate-induced striatal lesion in the rat. *Exp. Neurol.*, **2002**, *178*, 301-305.
- [156] Yamamoto, Y.; Tanaka, T.; Shibata, S.; Watanabe, S. Involvement of D1 dopamine receptor mechanism in ischemia-induced impairment of CA1 presynaptic fiber spikes in rat hippocampal slices. *Brain Res.*, **1994**, *665*, 151-154.
- [157] Okada, Y.; Sakai, H.; Kohiki, E.; Suga, E.; Yanagisawa, Y.; Tanaka, K.; Hadano, S.; Osuga, H.; Ikeda, J.E. A dopamine D4 receptor antagonist attenuates ischemia-induced neuronal cell damage via upregulation of neuronal apoptosis inhibitory protein. *J. Cereb. Blood Flow Metab.*, **2005**, *25*, 794-806.
- [158] Zou, S.; Li, L.; Pei, L.; Vukusic, B.; Van Tol, H.H.; Lee, F.J.; Wan, Q.; Liu, F. Protein-protein coupling/uncoupling enables dopamine D2 receptor regulation of AMPA receptor-mediated excitotoxicity. *J. Neurosci.*, **2005**, *25*, 4385-4395.
- [159] Hoffman, A.N.; Cheng, J.P.; Zafonte, R.D.; Kline, A.E. Administration of haloperidol and risperidone after neurobehavioral testing hinders the recovery of traumatic brain injury-induced deficits. *Life Sci.*, **2008**, *83*(17-18), 602-607.
- [160] Tang, Y.P.; Noda, Y.; Nabeshima, T. Involvement of activation of dopaminergic neuronal system in learning and memory deficits associated with experimental mild traumatic brain injury. *Eur. J. Neurosci.*, **1997**, *9*(8), 1720-1727.
- [161] Kobori, N.; Dash, P.K. Reversal of brain injury-induced prefrontal glutamic acid decarboxylase expression and working memory deficits by D1 receptor antagonism. *J. Neurosci.*, **2006**, *26*(16), 4236-4246.
- [162] Cohen, L.J. Risperidone. *Pharmacotherapy*, **1994**, *14*(3), 253-265.
- [163] Reimold, M.; Solbach, C.; Noda, S.; Schaefer, J.E.; Bartels, M.; Beneke, M.; Machulla, H.J.; Bares, R.; Glaser, T.; Wormstall, H. Occupancy of dopamine D(1), D (2) and serotonin (2A) receptors in schizophrenic patients treated with flupentixol in comparison with risperidone and haloperidol. *Psychopharmacology (Berl)*, **2007**, *190*(2), 241-249.
- [164] Schapira, A.H. Molecular and clinical pathways to neuroprotection of dopaminergic drugs in Parkinson disease. *Neurology*, **2009**, *72*(7 Suppl), S44-50.
- [165] Tatton, W.G.; Ju, W.Y.; Holland, D.P.; Tai, C.; Kwan, M. (-)-Deprenyl reduces PC12 cell apoptosis by inducing new cell synthesis. *J. Neurochem.*, **1994**, *63*(4), 1572-1575.
- [166] Tatton, W.G.; Greenwood, C.E. Rescue of dying neurons: a new action for deprenyl in MPTP parkinsonism. *J. Neurosci. Res.*, **1991**, *30*(4), 666-672.
- [167] Wu, R.M.; Chiueh, C.C.; Pert, A.; Murphy, D.L. Apparent antioxidant effect of l-deprenyl on hydroxyl radical formation and nigral injury elicited by MPP+ *in vivo*. *Eur. J. Pharmacol.*, **1993**, *243*(3), 241-247.
- [168] Zhu, J.; Hamm, R.J.; Reeves, T.M.; Povlishock, J.T.; Phillips, L.L. Postinjury administration of L-deprenyl improves cognitive function and enhances neuroplasticity after traumatic brain injury. *Exp. Neurol.*, **2000**, *166*(1), 136-152.
- [169] Newburn, G.; Newburn, D. Selegiline in the management of apathy following traumatic brain injury. *Brain Inj.*, **2005**, *19*(2), 149-154.
- [170] Mandel, S.; Weinreb, O.; Amit, T.; Youdim, M.B. Mechanism of neuroprotective action of the anti-Parkinson drug rasagiline and its derivatives. *Brain Res. Brain Res. Rev.*, **2005**, *48*(2), 379-387.
- [171] Huang, W.; Chen, Y.; Shohami, E.; Weinstock, M. Neuroprotective effect of rasagiline, a selective monoamine oxidase-B-inhibitor, against closed head injury in the mouse. *Eur. J. Pharmacol.*, **1999**, *366*(2-3), 127-135.
- [172] Gomez-Vargas, M.; Nishibayashi-Asanuma, S.; Asanuma, M.; Kondo, Y.; Iwata, E.; Ogawa, N. Pergolide scavenges both hydroxyl and nitric oxide free radicals *in vitro* and inhibits lipid peroxidation in different brain regions. *Brain Res.*, **1998**, *790*(1-2), 202-208.
- [173] Gu, M.; Iravani, M.M.; Cooper, J.M.; King, D.; Jenner, P.; Schapira, A.H. Pramipexole protects against apoptotic cell death by non-dopaminergic mechanisms. *J. Neurochem.*, **2004**, *91*(5), 1075-1081.
- [174] Vu, T.Q.; Ling, Z.D.; Ma, S.Y.; Robie, H.C.; Tong, C.W.; Chen, E.Y.; Lipton, J.W.; Carvey, P.M. Pramipexole attenuates the

- dopaminergic cell loss induced by intraventricular 6-hydroxydopamine. *J. Neural. Transm.*, **2000**, *107*(2), 159-176.
- [175] Nair, V.D.; Sealfon, S.C. Agonist-specific transactivation of phosphoinositide 3-kinase signaling pathway mediated by the dopamine D2 receptor. *J. Biol. Chem.*, **2003**, *278*(47), 47053-47061.
- [176] Du, F.; Li, R.; Huang, Y.; Li, X.; Le, W. Dopamine D3 receptor-preferring agonists induce neurotrophic effects on mesencephalic dopamine neurons. *Eur. J. Neurosci.*, **2005**, *22*(10), 2422-2430.
- [177] Hall, E.D.; Andrus, P.K.; Oostveen, J.A.; Althaus, J.S.; VonVoigtlander, P.F. Neuroprotective effects of the dopamine D2/D3 agonist pramipexole against postischemic or methamphetamine-induced degeneration of nigrostriatal neurons. *Brain Res.*, **1996**, *742*(1-2), 80-88.
- [178] Patrick, P.D.; Blackman, J.A.; Mabry, J.L.; Buck, M.L.; Gurka, M.J.; Conaway, M.R. Dopamine agonist therapy in low-response children following traumatic brain injury. *J. Child Neurol.*, **2006**, *21*(10), 879-885.
- [179] Onali, P.; Olanas, M.C.; Gessa, G.L. Characterization of dopamine receptors mediating inhibition of adenylate cyclase activity in rat striatum. *Mol. Pharmacol.*, **1985**, *28*(2), 138-145.
- [180] Weiss, S.; Sebben, M.; Garcia-Sainz, J.A.; Bockaert, J. D2-dopamine receptor-mediated inhibition of cyclic AMP formation in striatal neurons in primary culture. *Mol. Pharmacol.*, **1985**, *27*(6), 595-599.

Received: April 29, 2010

Revised: June 16, 2010

Accepted: September 15, 2010

© Bales et al.; Licensee Bentham Open.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.