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Review article

The neuroprotective potential of low-dose methamphetamine in preclinical models of stroke and traumatic brain injury

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ABSTRACT

Methamphetamine is a psychostimulant that was initially synthesized in 1920. Since then it has been used to treat attention deficit hyperactive disorder (ADHD), obesity and narcolepsy. However, methamphetamine has also become a major drug of abuse worldwide. Under conditions of abuse, which involve the administration of high repetitive doses, methamphetamine can produce considerable neurotoxic effects. However, recent evidence from our laboratory indicates that low doses of methamphetamine can produce robust neuroprotection when administered within 12 h after severe traumatic brain injury (TBI) in rodents. Thus, it appears that methamphetamine under certain circumstances and correct dosing can produce a neuroprotective effect. This review addresses the neuroprotective potential of methamphetamine and focuses on the potential beneficial application for TBI.

Contents

Abbreviations: ADHD, attention hyperactive disorder; AKT, protein kinase B; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Bcl-2, B-cell lymphoma 2; BDNF, brain derived neurotrophic factor; Css, Steady state plasma concentration; D1, type 1 dopamine receptor; D_2, type 2 dopamine receptor; DAT, dopamine transporter; FDA, Food and Drug Administration; IV, intravenous; MRI, magnetic resonance imaging; NAT, norepinephrine transporter; NMDA, N-methyl-D-aspartate; OGD, oxygen glucose deprivation; PET, positron emission tomography; PI3K, phosphoinositol 3 kinase; PV, parvalbumin; RHSC, rat hippocampal slice cultures; SERT, serotonin transporter; SST, somatostatin; TBI, traumatic brain injury; USP, United States Pharmacopeia; UTD, untreated; VMAT, vesicular monoamine transporter.

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1. Introduction

Methamphetamine has become a major drug of abuse worldwide. There is clear evidence that when ingested at high repetitive doses, methamphetamine produces measurable neurotoxicity (Ares-Santos et al., 2013; Ares-Santos et al., 2014; Cadet and Krasnova, 2009; Krasnova and Cadet, 2009). While there is considerable evidence that methamphetamine abuse produces detrimental CNS alterations, there is contrasting evidence that methamphetamine can produce neuroprotective effects. In a 2008 study, O'Phelan et al. reported that severe traumatic brain injury (TBI) patients that tested positive for

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methamphetamine at the time of admission, had a significant, though unexplained, decrease in mortality (odds ratio of 0.25 ($p = 0.02$)) (O'Phelan et al., 2008). In their discussion, the authors raised the point that methamphetamine may have both neurotoxic and neuroprotective capabilities. Interestingly, in a second study, O'Phelan et al. (2013) reported that TBI patients who tested positive for methamphetamine exhibited a significant (60%) reduction in pericontusional cerebral blood flow. These observations suggest that methamphetamine presents an interesting paradox of neuroprotection and neurotoxicity.

In the United States, 1.7 million individuals suffer from TBI every year. TBI represents a leading cause of disability worldwide. The annual costs of TBI have been estimated at $60 billion. Clearly there is a crucial unmet need to develop novel, effective therapies that can be administered within a clinically relevant therapeutic window following injury. Unfortunately, there are currently no approved therapeutic interventions available to prevent cognitive and behavioral deficits following TBI. However, our laboratory and others have begun examining the potential therapeutic benefits of methamphetamine. In this review we will highlight the potential mechanisms of neuroprotection activated by the controlled administration of low dose methamphetamine.

2. Preclinical studies

There has been a small but growing body of research supporting the use of amphetamines for the treatment of brain injury. Beginning in the early 1980's Hovda and Fenney performed studies in which a small dose (5 mg/kg) of amphetamine was administered during the chronic phase of injury to cats with motor cortex damage. They observed a significant reduction in motor deficits that was blocked by haloperidol, a preferential D_2 type antagonist (Feeney and Hovda, 1983; Hovda and Feeney, 1985). Hovda and Fenney went on to show that D-amphetamine, administered 10 days after frontal cortex damage in a cat, produced a significant, long-term improvement in motor cortex associated tasks (Hovda and Fenney, 1984; Hovda et al., 1989). Following these studies, Dhillon et al. (1998) demonstrated that amphetamine administration after TBI in rats reduced lactate levels as well as palmitic, stearic, oleic and arachidonic acids that typically lead to inflammation. In support of these findings, we recently reported that treatment with low dose methamphetamine (IV infusion with 0.5 mg/kg/h for 24 h) after severe TBI significantly reduced pro-inflammatory signals, which also correlated with significant improvements in functional and cognitive performance (Rau et al., 2014). Researchers have also demonstrated that amphetamine treatment increased both brain derived neurotrophic factor (BDNF) and synapsin I after a cortical contusion in rats, further suggesting potential neuroprotective effects for amphetamines (Griesbach et al., 2008).

3. Clinical studies

Based on these previous studies, one may conclude that amphetamines have significant potential as treatment for acute brain injury. However, the number of clinical trials that have utilized amphetamines is limited. Walker-Batson et al. (1995) found that 10 stroke patients that were given 10 mg of D-amphetamine every fourth day for 10 sessions and paired with physical therapy had a significant improvement in motor function compared to placebo treated controls. This effect was present up to one year even after amphetamine administration was discontinued. While this early study is encouraging, other subsequent small stroke trials have not been as successful. A recent review analyzed ten clinical trials conducted on stroke patients using D-amphetamine and found that only two reported a significant improvement in neurological outcomes (Harbeck-Seu et al., 2011). Interestingly, adverse events were reported in three trials. However, the numbers of adverse events were higher in the placebo groups than the D-amphetamine groups, suggesting that the D-amphetamine may not be responsible for generating an increase in adverse events (Harbeck-Seu et al., 2011). Concomitant medications and secondary medical interventions are principal co-variables in stoke studies that are difficult to control or evaluate in trials of small size. The seven other trials did not list any adverse events associated with D-amphetamine administration.

A second issue with these trials involved the dosing regimen coupled to physical training. Many of the trials administered D-amphetamine once or twice a week in small doses as part of a physical rehabilitation study that involved a small cohort of patients (mean = 21). Given the wide range of ages and the varied sequelae associated with stroke, it may be useful to perform a larger study in which treatment is initiated during the acute injury phase and carried out through the rehabilitation period with consistent rehabilitation methods. Supporting this possibility, Goldstein conducted an assessment of amphetamine trials in stroke and concluded, "*The variable and largely negative clinical trial results could be attributable to design factors related to stroke location and extent, the dosing and timing of the drug, and the type, intensity, and timing of physiotherapy.*" (Goldstein, 2009).

4. Pharmacology

Methamphetamine has been approved as a therapeutic compound by every world regulatory agency. As a consequence, we now have decades of clinical information associated with methamphetamine as the prescription oral drug product Desoxyn® [methamphetamine HCl tablets, United States Pharmacopeia (USP)]. In this formulation, methamphetamine is used as a secondary treatment for attention deficit hyperactivity disorder (ADHD) in children over the age of six and for the short-term management of exogenous obesity. Used in this context, the FDA has approved the administration of methamphetamine at doses of up to 25 mg/day. In addition, up to 60 mg/day of methamphetamine has been used in the treatment of narcolepsy (Mitler et al., 1993). At low-to-moderate doses (5–30 mg), methamphetamine-induced responses include arousal, reduced fatigue, euphoria, accelerated heart rate, elevated blood pressure, pupil dilation, increased temperature, reduced appetite, behavioral disinhibition and short-term improvements in cognition. At higher doses (≥30 mg) neuropsychological effects, such as anxiety can be observed (Cruickshank and Dyer, 2009). Previous studies indicate that methamphetamine toxicity occurs when plasma levels reach a range of 200–5000 ng/ml (Cruickshank and Dyer, 2009). To avoid toxicity, current FDA guidelines consider acceptable dosing (for both adults and children) at 25 mg within a 24-hour period. Based on this guideline, dosing an average seven-year-old (weighing approximately 25 kg) at 1 mg/kg for 24 h would achieve the FDA-approved oral dose limit. In pharmacokinetic studies conducted in our laboratory, rats receiving methamphetamine at 0.5 mg/kg/h (infused over a period of 24 h) produced a steady-state concentration of approximately 25 ng/ml. This plasma level produced significant improvements in cognition and functional behavior following severe TBI in rats (Rau et al., 2012, 2014). In humans, the oral bioavailability of methamphetamine is approximately 70% but increases to 100% following intravenous (IV) delivery (Ares-Santos et al., 2013). In order to achieve a comparable therapeutic plasma methamphetamine target level of 25 ng/ml as observed in rats, a 70 kg adult would need a total dose of 17.9 mg.

Thus, it appears that a target steady state concentration (Css) of 25 ng/ml and the doses required to achieve it are substantially less than the current approved dosing for clinical application within the United States. By comparison, methamphetamine concentrations are substantially higher in recreational abusers. Various pharmacokinetic studies have demonstrated that methamphetamine levels in recreational abusers (via various routes of administration) are commonly in excess of those seen under recommended clinical guidelines (Cruickshank and Dyer, 2009). Peak concentrations of approximately 100 ng/ml or greater are routinely observed in drug abusers (Cruickshank and Dyer, 2009). Self-administration of methamphetamine in drug abuse is typically

through the repetitive oral doses of 100 to 150 mg (Cruickshank and Dyer, 2009).

Distribution studies with methamphetamine indicate that the drug is rapidly absorbed into the brain. Methamphetamine exhibits high lipophilicity (due to the methyl group) that yields a high tissue to plasma ratio (Cruickshank and Dyer, 2009). Recent studies utilizing MRI and PET imaging techniques in human volunteers revealed an equilibration brain to blood ratio of >8 (Volkow et al., 2010). These studies indicate an elimination half-life for methamphetamine on the order of 9 to 13 h (Volkow et al., 2010). Thus, methamphetamine has a unique ability to rapidly penetrate into the brain with a high tissue partitioning and persist for extended periods. These properties, when combined with its neuroprotective properties, impart unique characteristics making it potentially useful for treating injuries such as TBI, where rapid and persistent intervention is critical to clinical outcomes.

5. The potential role of monoamines in neuroprotection and neurotoxicity

Amphetamine and methamphetamine reverse the function of vesicular monoamine transporters (VMAT) as well as the cell surface transporters for dopamine (DAT), norepinephrine (NET) and serotonin (SERT) (Cruickshank and Dyer, 2009). This results in a redistribution of dopamine, norepinephrine and serotonin from intracellular stores into the synaptic cleft. Thus, methamphetamine serves as an indirect agonist for dopamine, norepinephrine and serotonin receptors. In addition, methamphetamine attenuates the metabolism of these monoamines by inhibiting monoamine oxidase, which results in prolonged neuronal signaling (Cadet et al., 2007; Krasnova and Cadet, 2009).

In an effort to further elucidate the effect of each monoamine, we used an in vitro stroke model to assess the effect of dopamine, norepinephrine and serotonin in regard to neuroprotection and neurotoxicity. Using organotypic, rat hippocampal slice cultures (RHSC) exposed to 60 min of oxygen glucose deprivation (OGD), we performed a dose–response study in which each monoamine, at various concentrations, was placed into the media during the recovery phase (Rau et al., 2011). We utilized propidium iodide as an indicator of cell death to assess potential neuroprotection (Rau et al., 2011). In these studies, serotonin significantly reduced neuronal loss when added at concentrations of 10 nM–100 μM (Fig. 1). Interestingly, when 1 mM serotonin was added to the OGD-exposed cultures, there was a significant increase in neuronal death compared to the untreated slices exposed to OGD. This finding suggests that serotonin may play a key role in methamphetamine-mediated neurotoxicity associated with high dosing.

Norepinephrine induced significant protection when added to slice cultures at concentrations of 10–100 nM. However, at higher concentrations of 100 μM or 1 mM no significant neuroprotective effect was observed. Unlike serotonin, the higher concentrations of norepinephrine did not produce an increase in neuronal death. While high doses of serotonin and norepinephrine produced toxicity or failed to protect cells respectively, the highest concentrations of dopamine produced the most robust dose-dependent neuroprotection. Taken together, these data suggest that methamphetamine may mediate neuroprotection, at least in part, through a dopamine-dependent signaling mechanism(s). It further suggests that many of the previous studies that have attributed methamphetamine-mediated neuropathology to reactive oxygen species (ROS) generated via excess dopamine metabolism may not be considering the potential neuropathological effects of serotonin. In further support of our findings, Hirata et al. (1995) demonstrated a serotonin dependent increase in superoxide radicals following the administration of a high dose of methamphetamine (10 mg/kg every 2 h for four injections). Conversely, a similar response was not observed with a lower dose (5 mg/kg every 2 h for four injections), further reiterating the potential dose-dependent difference between methamphetamine-mediated neuroprotection and neurotoxicity (Hirata et al., 1995).

6. The neuroprotective effects of dopamine

The potential role of dopamine in protection from excitotoxicity was suggested more than a decade ago when Lee et al. (2002) used rat primary hippocampal neuronal cultures to demonstrate a direct interaction between D1 dopamine and NMDA receptors. The authors showed that dopamine activation of D1 receptors resulted in reduced Ca^{2+} permeability of NMDA receptors, the activation of phosphoinositol-3 kinase (PI3K) and improved cell survival (Lee et al., 2002). Three years later, Zou et al. (2005) demonstrated that D2 dopamine receptors indirectly interact with AMPA receptors. Dopamine mediated activation of D2 receptors resulted in the internalization of AMPA receptors, which also activated PI3K kinase signaling, the phosphorylation of protein kinase B (AKT), an upregulation of Bcl-2 expression and a reduction in apoptotic cell death (Zou et al., 2005). Confirming these observations, we recently reported that methamphetamine-mediated neuroprotection was significantly reduced in vitro with either D1 or D2 receptor antagonists (Rau et al., 2011). We also demonstrated that methamphetamine-mediated neuroprotection was blocked by PI3K inhibitors. Furthermore, we reported that methamphetamine-mediated PI3K activation results in enhanced phosphorylation of AKT and cell survival (Rau et al., 2011). In addition to our studies, Vaarmann et al. (2013) recently demonstrated that dopamine prevented delayed calcium dysregulation as a consequence of glutamate-mediated excitotoxicity. This effect was again dependent on the activation of D_1 and D_2 receptors and was enhanced by the addition of a monoamine oxidase inhibitor (Vaarmann et al., 2013).

While it is known that all three monoamines are affected by amphetamine and methamphetamine, it appears that this class of stimulants has the greatest impact on dopamine signaling. Amphetamine increases dopamine in the synaptic cleft as well as blocking reuptake at the dopamine transporter (DAT) (Miller, 2011). Amphetamine also affects

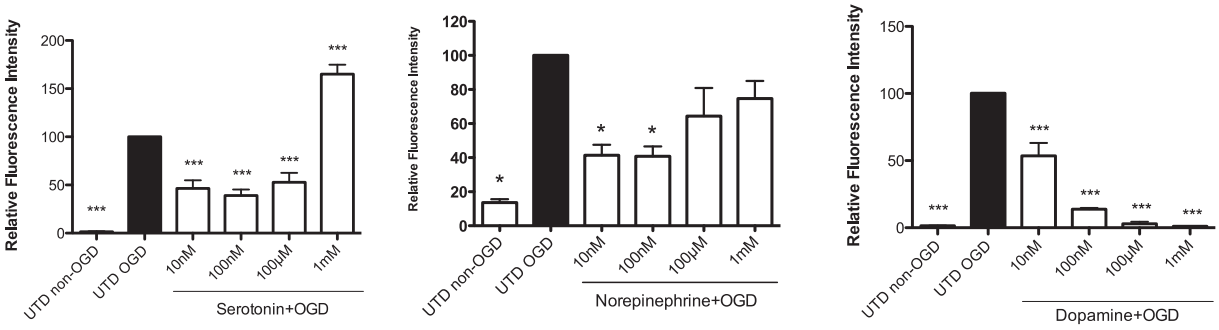

Fig. 1. Monoamines induce a dose dependent neuroprotective response in an in vitro model of stroke. Rat hippocampal slice cultures were exposed to 60 min of oxygen/glucose deprivation (OGD) and either untreated (UTD) or exposed to graded concentrations (10 nM–1 mM) of serotonin, norepinephrine or dopamine. Relative fluorescence intensity was measured based on propidium iodide staining of dead neurons. *p < 0.05; **p < 0.01; ***p < 0.001. Statistical analysis was done as ANOVA with Tukey post-hoc analysis.

the presynaptic neuron by activating TAAR1, which induces DAT phosphorylation through protein kinase A and C (Miller, 2011). This, in turn, results in a reverse transporter function of DAT, allowing further efflux of dopamine into the synaptic cleft (Miller, 2011).

The role of dopamine signaling in cognition is directly linked to the striatum, a structure that is commonly damaged in both stroke and TBI. PET neuroimaging studies in humans have demonstrated a critical role for the striatum in cognitive performance (Marie et al., 1999). Patients with Parkinson's disease assessed using 18F-dopa were found to have a correlation between dopamine depletion and decreased neuropsychological performance (Broussolle et al., 1999; Duchesne et al., 2002; Marie et al., 1999). In further PET imaging studies, a correlation was found between decreased striatal D_2 receptor activity and poor performance on tasks measuring executive function, attention, and working memory (Backman et al., 1997). Supporting this finding is a recent study in humans that examined the effect of amphetamines on cognitive flexibility. The researchers in this study found that amphetamine administration improved cognitive flexibility and this effect was dependent on dopamine activity within the thalamocorticostriatal network. They also found that the cognitive effect of amphetamines was more pronounced in individuals that had higher baseline levels of dopamine receptors in the thalamus and cortex and greater striatal dopamine release (Samanez-Larkin et al., 2013).

7. Dose dependent effects of amphetamine and methamphetamine

There is clear evidence that amphetamine and methamphetamine induce the release of dopamine through multiple mechanisms. Fleckenstein et al. (2007) proposed the "exchange-diffusion model" in which amphetamines bind to the extracellular site on DAT and compete with extracellular dopamine. DAT transports dopamine in a bi-directional manner, and intracellular concentrations of dopamine are higher under normal physiological conditions (Fleckenstein et al., 2007). Thus, binding of amphetamines causes reverse transport of cytosolic dopamine outside of the cell (Panenka et al., 2013). Fleckenstein et al. (2007) also proposed the "weak base hypothesis," which suggests that as weak bases, amphetamines can reduce the vesicular membrane pH gradient, compromising VMAT-2 activity and reducing vesicular sequestration of dopamine. However, it has been suggested that high concentrations of amphetamine (>100 μM) would be required to accomplish this effect (Schwartz et al., 2006). More recently Siciliano et al. (2014) demonstrated that low concentrations (10 nM) of amphetamine cause DAT-dependent dopamine release. In contrast, the authors also showed that higher concentrations of only 10 μM amphetamine induced dopamine release via a DAT-independent mechanism. These data further support the idea that low doses of amphetamines are insufficient to disrupt vesicular sequestration and act solely as inhibitors of DAT (Siciliano et al., 2014).

While both methamphetamine and amphetamine increase DAT-mediated dopamine efflux, these compounds can exert quite different effects on neurons. Using an in vitro expression system, Goodwin et al. (2009) reported that methamphetamine released five times more dopamine than amphetamine in a DAT dependent manner. The authors further demonstrated that methamphetamine induced the release of twice as much Ca^{2+} from intracellular stores compared to amphetamine (Goodwin et al., 2009). Recently, Saha et al. (2014) demonstrated that amphetamine and methamphetamine differentially affect DAT activity and spontaneous firing of dopaminergic neurons (Saha et al., 2014). Using cultured midbrain dopaminergic neurons, the authors presented evidence that methamphetamine was less effective at increasing the spontaneous firing of these neurons. When added at equal concentrations (1 μM), methamphetamine induced significantly less inward current than amphetamine (Saha et al., 2014). Interestingly, Saha et al. (2014) further demonstrated that intracellular methamphetamine, but not intracellular amphetamine, significantly attenuated the increase in dopaminergic neuron firing following the addition of extracellular dopamine. Importantly, these authors further demonstrated that while both amphetamine and methamphetamine induced DAT-mediated inward currents were equally Na^+-dependant, they also demonstrated that amphetamine-induced DAT-mediated inward currents were preferentially Cl^--dependent (Saha et al., 2014).

As previously discussed, clinically low doses of methamphetamine have been used to enhance cognition and treat ADHD. Recently, Branch and Beckstead (2012) demonstrated the bidirectional and concentration dependent effect of methamphetamine on dopaminergic neuron activity. Using mouse midbrain slices, these authors demonstrated that low concentrations (300 nM) of methamphetamine not only enhanced dopamine neuron firing through DAT-mediated conductance, but also enhanced the amplitude of dopamine-mediated inhibitory post-synaptic currents (IPSCs). In contrast, higher concentrations (10 μM) of methamphetamine reversed both of these effects (Branch and Beckstead, 2012). Collectively, these data provide further strong support for the concentration dependent effects of methamphetamine on neuroprotection and neurotoxicity.

8. Impact of amphetamines on cognition and neurogenesis

While the clinical value of amphetamines in neuromotor rehabilitation remains in question, there is evidence that suggests amphetamines may enhance cognition and play a role in recovery of cognitive function after acute brain injury. Walker-Batson et al. (1992) examined the potential of amphetamine treatment to improve aphasia in stroke patients. Again, only a small number of patients were examined (6 patients total). However, the authors reported that 5 out of 6 patients performed better than expected on the Porch Index at six months post-stroke (Walker-Batson et al., 1992).

Using a low dose regimen (a single IV infusion of 0.5 mg/kg/h for 24 h) we observed a significant enhancement in learning and memory in uninjured (sham) rats when compared to uninjured saline treated rats (performance was assessed 42 days after treatment) (Rau et al., 2012). Using a different dosing regimen Moenk and Matuszewich (2012) also reported that low dose methamphetamine produced a significant and long-term effect on cognitive behavior in uninjured rats. In their studies, these authors administered once daily injections of 2 mg/kg for 15 days to juvenile rats (post-natal day 20–34). Performance in the Morris water maze was then assessed approximately 45 days after treatment. Interestingly, under these dosing conditions, the significant improvement in Morris water maze performance was only observed when juvenile rats were treated. Adult rats (post-natal day 70–84) treated with this same dosing regimen did not exhibit significant improvements in learning (Moenk and Matuszewich, 2012).

TBI and stroke often impact the hippocampus, which is critical to learning and memory. Traditionally, the hippocampus has been studied in terms of glutamate signaling. However, dopaminergic inputs play a key role in the modulation of hippocampal function (Hansen and Manahan-Vaughan, 2014). It has been demonstrated that dopamine receptors in the hippocampus facilitate the maintenance of long-term potentiation (LTP) through projections from the subthalamic nucleus (Takahashi, 2013). This is a factor in cognitive performance as the facilitation of LTP in the hippocampus is a critical step in memory formation and consolidation (Lemon and Manahan-Vaughan, 2006). There is also evidence that dopamine receptor activation may spare neurons in the hippocampus after TBI. Kline et al. (2004) administered bromocriptine, a D_2 receptor agonist, to rats 15 min prior to exposure to a TBI. Results from this study concluded that bromocriptine administration resulted in a significant increase in CA3 neuronal survival as well as reduced memory deficits (Kline et al., 2004). Furthermore, our own studies revealed that the administration of low dose methamphetamine significantly preserved CA1 neurons following severe TBI (Rau et al., 2012, 2014).

We recently demonstrated that methamphetamine significantly enhanced learning and memory following TBI (Rau et al., 2012, 2014). Supporting this finding, a second study demonstrated that increasing dopamine release and blocking reuptake using amantadine significantly reduced cognitive impairment in TBI rats (Wang et al., 2014). We have

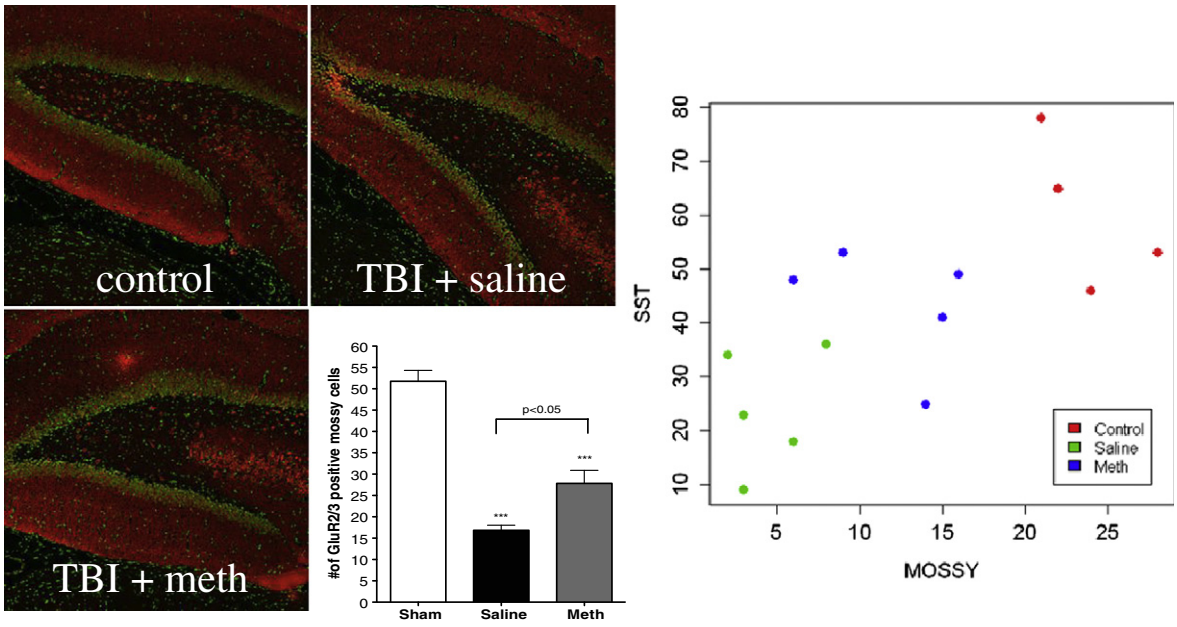

Fig. 2. Methamphetamine treatment preserves mossy cells within the hippocampus hilar region. Mossy cells in paraffin embedded brain sections were stained with anti-GluR2/3 antibody (red) and neurons were stained with neurotrace (green). ***$p < 0.001$ relative to uninjured controls (shams). Scatter plot at right shows pairwise comparison between mossy cell numbers and SST positive inhibitory interneuron numbers in uninjured controls (red dots), methamphetamine treated TBI rats (blue dots), and saline treated TBI rats (green dots).

also showed that methamphetamine treatment significantly enhanced neurogenesis of granule neurons in the hippocampus following severe TBI (Rau et al., 2012). Recent evidence indicates that mossy cells are the first glutamatergic neurons to make contact with newborn granule neurons (Chancey et al., 2014). Mossy cells also provide considerable feed forward inhibition onto granule neurons via parvalbumin (PV) and somatostatin (SST) positive inhibitory interneurons. However, mossy cells are also extremely vulnerable to injury and damage following stroke or TBI (Chancey et al., 2014). The preservation of these cells as well as PV or SST positive inhibitory interneurons is likely to have a profound impact on granule neuron signaling and learning/memory.

Mossy cells receive considerable monoamine input (Harley, 2007; Jinde et al., 2013). Based on these structural connections we attempted to determine if methamphetamine treatment could preserve mossy cells following severe TBI. We observed a significant preservation of mossy cells 48 h after TBI when low dose methamphetamine was administered beginning 8 h after injury (Fig. 2). Furthermore, while methamphetamine treatment had no effect on the preservation of PV cells, we did observe a significant reduction in SST inhibitory neuron loss following TBI (Fig. 2).

9. Conclusion

There is clear evidence that methamphetamine, in high repetitive doses, produces neuropathology. However, the characteristics and mechanisms that make it a highly addictive drug of abuse, also impart value as a potential therapeutic intervention for acute brain injury. Methamphetamine crosses the blood brain barrier rapidly and in low doses produces very few side effects. In the brain, methamphetamine potently increases dopamine signaling throughout the cortex, striatum and hippocampus. Furthermore, methamphetamine has a relatively long half-life in humans and thus high concentrations are not necessary to achieve a therapeutic effect. Also, methamphetamine is metabolized to amphetamine, which further prolongs the active effects in the brain.

In all of our studies using *low dose* methamphetamine we have not found any evidence of neuropathology caused by the drug treatment. To the contrary, we have observed a reduction in neuronal loss, apoptotic cell death, and neuromotor/cognitive impairment after acute brain injury. In light of the fact that low dose methamphetamine is FDA approved for use in juveniles and adults, we see no valid reason why it cannot be utilized in human clinical trials for stroke and TBI. We propose that low dose methamphetamine has significant potential as a neuroprotective agent when the dosing is kept within safe, previously established guidelines.

Acknowledgments

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