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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 ($\geq$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

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