Acta Pharmacologica Sinica (2013) 34: 1485–1490
 1671-4083/13
www.nature.com/aps

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Review

The neuroprotective effects of progesterone on traumatic brain injury: current status and future prospects

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Traumatic brain injury is the leading cause of morbidity and mortality in young adults. The secondary injury in traumatic brain injury consists of a complex cascade of processes that simultaneously react to the primary injury to the brain. This cascade has been the target of numerous therapeutic agents investigated over the last 30 years, but no neuroprotective treatment option is currently available that improve neurological outcome after traumatic brain injury. Progesterone has long been considered merely a female reproductive hormone. Numerous studies, however, show that progesterone has substantial pleiotropic properties as a neuroprotective agent in both animal models and humans. Here, we review the increasing evidence that progesterone can act as a neuroprotective agent to treat traumatic brain injury and the mechanisms underlying these effects. Additionally, we discuss the current progress of clinical studies on the application of progesterone in the treatment of traumatic brain injuries.

Keywords: progesterone; traumatic brain injury; neuroprotection; hormone

Acta Pharmacologica Sinica (2013) 34: 1485–1490; doi: 10.1038/aps.2013.160; published online 18 Nov 2013

Introduction

Traumatic brain injury (TBI) is one of the leading causes of injury-related death and severe disability worldwide, resulting in large direct and indirect costs to society. While the clinical management of TBI has been greatly improved with the development of standardized approaches to care, no medical treatment adjuncts have been proven to be effective in reducing mortality or limiting disability following TBI [1]. Progesterone (PROG) has long been considered merely a female reproductive hormone with little role in neuroprotection after brain injury. In fact, PROG is a neurosteroid that has many complex properties affecting the mechanisms involved in neuroprotection and repair after various types of brain injury[2].

Overview of neuroprotective agents in TBI

TBI results in both primary and secondary injuries. Primary injuries are those injuries that immediately result from the initial impact or insult. In contrast, a secondary brain injury is a delayed response that results from a complex group of cellular and molecular responses to the primary injury. These are characterized by a complex cascade of molecular and biochemical events that lead to neuro-inflammation, brain edema, and delayed neuronal death. Both primary and secondary injuries can ultimately result in cell death and irreversible damage.

In recent decades, our understanding of the cellular and molecular changes that occur after TBI has significantly increased. A number of new potential therapeutic targets have been identified which may enable the prevention of the onset or a reduction in the extent of secondary brain injuries. Currently, the mainstay of therapy for TBI is the removal of hematomas and the repair of significant skull fractures, along with supportive therapies aimed at maintaining perfusion and oxygenation to tissues. For patients who do not have operable lesions, the control of ICP (<20 mmHg), cerebral perfusion pressure (CPP, >60 mmHg) and systemic, and perhaps local, oxygenation are the cornerstones of intensive care unit management. Other necessary medical interventions are commonly employed, such as early enteral nutrition, maintenance of fluid volume, and prevention and treatment of complications, such as hyperthermia, hypernatremia, seizures, pneumonia, venous thromboembolism and stress-related mucosal bleeding[3]. Many of these therapies can influence the outcome for a TBI patient.

Because the primary injury is considered irreversible, the

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Received 2013-06-24 Accepted 2013-09-28

major opportunity for interventions that could prevent further neurological decline is in reversing or preventing secondary injuries. After decades of research, a number of experimental TBI models have been developed to study the mechanisms that occur following trauma, and many potential therapeutic interventions have been developed. In these preclinical studies, numerous pharmacological treatments have been identified, with at least 30 compounds and therapeutic interventions being the subject of more than 50 clinical trials over the last three decades. However, despite the encouraging preclinical results, none of these investigations have lead to any considerable improvement in the clinical outcome[4].

Most of the promising therapeutic strategies derived from experimental animal studies have failed when they are translated into the clinical setting of TBI. Glucocorticoids, once a mainstay of TBI treatment, are now known to be harmful[5, 6]. The trial of magnesium sulfate was stopped when it was found that the magnesium sulfate treatment group had a significantly higher mortality rate than the control group[7]. More recently, citicoline, an endogenous substance offering potential neuroprotective properties that facilitates neurorepair after injury, was also shown to not improve the clinical function and cognitive status of patients after injury[8].

The underlying reason for this disappointing failure likely varies from case to case. First, most injury models used to simulate TBI only represent the relatively homogenous injury types, while in reality, TBI is quite heterogenous. Clinical trials usually include a range of injury severities, whereas preclinical studies only use well-defined, highly controlled animal models of preselected severity. These conceptual and methodological issues should contribute to the difficulty in translating promising preclinical findings into human application.

Second, a detailed description of the therapeutic window, the pharmacokinetics, and the pharmacodynamics for each agent is not always available. Most animal studies use either pretreatment or very early treatment protocols, and such early intervention is not always possible in clinical TBI. Another popular problem for preclinical studies is the lack of pharmacokinetic or pharmacodynamic profiles of the drugs being examined or the levels of the drugs in the brain in relation to its therapeutic actions[9].

Third, drug dosing schedules usually differ between preclinical and clinical trials, with the latter frequently using lower doses (to avoid potential toxicity) combined with more frequent dosages (*eg*, continuous infusions) that have not been supported by the preclinical data.

Finally, another major issue is that most of these preclinical studies have focused on a single component of a complex TBI cascade, which neglects the complexity and diversity of secondary injury mechanisms. To address this issue, therapeutic strategies that target multiple delayed injury factors by either combining agents that have complementary effects or using multipotential drugs that modulate multiple injury mechanisms should be considered. Thus, the simultaneous targeting of several injury factors using pleiotropic drugs may maximize the likelihood of developing a successful therapeutic intervention to improve the outcome of TBI patients. This recognition has led to the recent emphasis on pleiotropic neuroprotection.

Preclinical studies of PROG in TBI

It is now clear that biological sex alters the incidence and outcome of ischemia and TBI. Stroke risk increases with age in both sexes, and there is broad evidence that the outcome of an ischemic event is worse in older women than in their male counterparts. This sexually dimorphic disease pattern remains apparent in women well beyond their menopausal years[10, 11]. In most animal experimental reports, the females tend to recover better than males following TBI[12, 13]. The serendipitous discovery that gender and menstrual cycle may have an effect on an animal's response to experimental TBI ultimately led to the development of PROG as a neuroprotective agent.

PROG is a steroid hormone that is well known for its role in the menstrual cycle. It is produced by the ovaries and the placenta in females, as well as by the brain, and it plays a critical role in neuronal development during gestation. In the brains of males and females, PROG is synthesized by oligodendrocytes and some neurons in roughly equal amounts[14, 15]. PROG receptors are widely expressed in the developing and adult brain, so various brain regions are the normal targets of PROG[16]. Indeed, the 10-fold increase in PROG synthesis during fetal growth is considered an evolutionary mechanism of PROG to protect the fetus during gestation. Because many processes involved in CNS repair after brain injury are thought to recapitulate what occurs during normal brain development[17], PROG may be actively involved in TBI recovery.

After three decades of extensive research on the use of PROG in TBI, it is clear that PROG is a neurosteroid that affects multiple mechanisms involved in neuroprotection and repairation after various types of brain injury[2, 17, 18]. There are currently more than 200 articles reporting the neuroprotective effects of PROG. PROG has been tested in four species, including humans, and in 22 different injury models, including TBI, stroke, spinal cord injury and neurodegenerative disorders. Overall, all the findings from the various studies show that PROG infusion results in reduced neuronal loss, enhanced remyelination, improved functional recovery, and an overall decrease in cerebral edema[2].

Clinical studies of PROG in TBI

Consistent with these promising preclinical studies, the first clinical study further supported the promise of PROG in the treatment of TBI[19]. This clinical research study was a single-center, open clinical trial that recruited 56 acute severe TBI patients (Glasgow Coma Scale≤8). Patients in the treatment group were given PROG via intramuscular injection at 1.0 mg/kg per 12 h for 5 consecutive days. The neurological outcomes of the patients were assessed using the Glasgow Outcome Scale (GOS), the verbal and motor functions scale and the Karnofsky Performance Scale (KPS). Follow-up assessment at 3 months found that the GOS, verbal functions and KPS in the PROG treatment group were more improved

than those in the control group. These results indicated that successive early application of PROG would be beneficial in the treatment of TBI patients. This clinical trial, which was performed by a Chinese hospital, had certain weaknesses, such as a small number of patients, the single-centered, open trial design, and the lack of long-term follow up. Despite these issues, it is the first publication of a clinical study evaluating PROG in the treatment of TBI patients.

Subsequently, two randomized, double-blind, placebo-controlled phase II clinical trials for PROG have been conducted[20, 21]. Though distinct differences were noted between these two clinical trials, such as inclusion criteria, dosage of progesterone, administration route, and the duration of follow up, both studies have shown decreases in mortality following PROG treatment, as well as improvements in functional outcome after severe injury (Table 1). The two studies also confirmed that the drug is safe and tolerated by the head injury patients. In Wright's ProTECT II clinical trial, compared to the controls, PROG treatment produced a 50% reduction in mortality at 30 d (rate ratio 0.43; 95% confidence interval 0.18 to 0.99). The improvement reflected by the Disability Rating Scale (DRS) outcome at 30 days was even more encouraging for patients with moderate injuries (P<0.02)[21]. Wright's findings were confirmed by Xiao's clinical trial[20]. In Xiao's study, it was found that PROG treatment significantly improved survival, as well as functional outcomes, at both 3 and 6 months. At 3 months, 47% of the PROG treated patients displayed better GOS functional outcomes compared to the 31% of the placebo patients (P=0.034). At 6 months, the number was 58% for the PROG group compared to the 42% of the placebo group (P=0.048). The 6 month mortality rate for the PROG group was 18%, whereas it was 32% for the placebo group (P=0.039).

Mechanisms underlying PROG's neuroprotective effects

PROG possesses pleiotropic effects that may markedly attenuate the injury cascade associated with TBI. Investigation into the cellular and biochemical pathways affected by PROG provided reasonable explanations for its efficacy in mitigating the effects of neuronal injury. Microarray analysis discovered that PROG influences the expression of approximately 500 genes involved in regulating inflammation, apoptosis and vascular remodeling, which support the pleiotropic properties of PROG as a hormone[22]. Additionally, PROG acts on multiple proteins and receptors, making it a candidate for potent therapies.

Edema

PROG has been reported to reduce both vasogenic and cytotoxic edema after TBI[23, 24]. It was found that the serum levels of PROG were inversely correlated with the degree of TBI-induced edema[25]. The underlying mechanisms by which PROG reduced the edema have not been fully elucidated, although several possible mechanisms have been proposed. PROG may decrease the levels of aquaporin 4 (AQP4), a water channel membrane protein that can, in turn, modulate cerebral edema[26], inhibit active ion uptake through the Na^+/K^+-ATPase and vessel growth associated with leaky blood– brain barrier function after TBI, modulate the vasopressin level, and reduce neurogenic inflammation[27]. All of these responses can help reduce cerebral edema after TBI and can lead to better functional outcomes[28].

Lipid peroxidation and oxidative stress

There is evidence that PROG can reduce lipid peroxidation through the inhibition of free radical formation and by enhancing scavenger efficiency to more vigorously eliminate reactive oxygen species[29]. This anti-oxidative stress effect is achieved by upregulating antioxidant enzymes, such as superoxide dismutase (SOD)[30], and by increasing the levels of mitochondrial glutathione, a critical free radical scavenger[31]. Reducing the presence of reactive oxygen and nitrogen species can help maintain membrane integrity and help stabilize the blood-brain barrier (BBB), which in turn improves cell survival following brain injury.

Inflammation

A number of studies have reported that PROG inhibits inflammation by modulating cytokine release and by inhibiting immune cell activation and migration[32–34]. PROG can reduce

Table 1. Two independently conducted, randomized, double-blind, placebo-controlled phase II clinical trials used to assess the efficacy of progesterone in TBI patients.

Characteristics	Wright *et al*[21]	Xiao *et al*[20]
Country	US	China
Glasgow coma scale (GCS)	4 to 12	≤8
Time after injury	<11 h	<8 h
Delivery method (length)	Intravenous (3 d)	Intramuscular (5 d)
Outcome assessment post-injury	30 d	3 and 6 months
Randomization (progesterone:placebo)	4:1	1:1
Patients	100	159
Progesterone	77	77
Placebo	23	82
Primary endpoint	GOS-E; DRS and Mortality	GOS; Mortality and the modified FIM

GOS, glasgow outcome scale; GOS-E, glasgow outcome scale-extended; DRS, disability rating scale; FIM, functional independence measure.

the injury-induced mRNA upregulation of interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNFα)[35]. In the central nervous system, PROG inhibits TNFα–induced microglia activation, and decreases microglial expression of iNOS and secretion of IFNγ, TGF-β2, and NO, thus leading to a reduction in neural degeneration and apoptosis[36]. PROG treatment following TBI significantly decreased the levels of complement factors 3 and 5, macrophage-inducing factor-1, and CDs 24 and 74. Additionally, administering PROG shortly after CNS injury reduced both the migration and proliferation of immune cells[37].

Apoptosis

PROG limits neuronal apoptosis by stabilizing the mitochondria. It can inhibit the activity of the mitochondrial-specific proapoptotic enzymes, such as cytochrome c, activated caspase-3, and the Bcl-2- associated death-promoter, and upregulate the anti-apoptotic versions of bcl-2 and the antiapoptotic protein ERK[38, 39]. By modulating mitochondrial function, PROG can help to maintain cellular integrity and survival.

Myelin repair and neurotrophic support

PROG can promote both central and peripheral remyelination by increasing myelin production[40–42]. PROG treatment stimulates the synthesis of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), at both the mRNA and protein levels[39, 40]. Thus, PROG may prove to be a potential treatment for certain neurodegenerative disorders, such as multiple sclerosis[43]. Additionally, PROG increased the expression of nerve growth factor (NGF) in the brain, which correlates with post-TBI benefits including the attenuation of cholinergic cell death, promotion of axonal growth, prevention of axotomy-induced neuronal loss, and inhibition of neuronal apoptosis[44].

Excitotoxicity

PROG can attenuate neuronal excitotoxicity[45] by blocking calcium channels[46] or by upregulating GABA, an inhibitory neurotransmitter in the CNS[47]. GABA mediated inhibition can then decrease the excessive injury induced excitotoxicity through the release of glutamate or other excitatory neurotransmitters[48].

Questions and prospects for phase III trials

Although most preclinical studies and several promising clinical trials have reported benefits of PROG treatment, no beneficial effects were detected in three recent studies in which PROG was applied to animal models of spinal cord contusion injury, ischemic stroke or "moderate" unilateral contusion of the parietal cortex[49–51]. Despite the numerous studies that support the use of PROG in the treatment of brain injuries, some scientists still argue that the results of the PROG neuroprotection studies are too good to be true for a "gestational" hormonal agent that has been known for such a long time in the reproductive physiology and animal husbandry fields. Many researchers even believe that PROG has already failed the criteria of neuroprotection in its preclinical stage[52, 53].

Currently, all TBI clinical trials have failed in Phase III. It is reasonable to have some pessimism about the success of PROG, although the phase II clinical trials did show great promise. It should be emphasized that the Phase II trials reported above were small, single-centered clinical studies with a small number of recruited patients. The randomization of the placebo group:PROG group was 1:4 in Wright's ProTECT II trial. With a small number of placebo patients serving as controls, small outcome shifts in a few patients could result in huge, sometimes opposite, switches in the conclusions. More critically, no long-term assessment of the neurological outcome is available for these studies yet.

To expand the Phase II findings, two major Phase III trials were initiated in 2010. ProTECT III (progesterone for traumatic brain injury: experimental clinical treatment), initiated by Emory University and sponsored by the NIH, has been recruiting patients from 31 TBI clinical centers across the United States. SyNAPSe, initiated by BHR, a branch of Besins Pharma, in collaboration with the American Brain Injury Consortium (ABIC) and the European Brain Injury Consortium (EBIC), is another Phase III study investigating the efficacy and safety of progesterone in patients with severe traumatic brain injuries. SyNAPSe is a registration study and is designed to fulfill the requirements of the FDA for a future New Drug Application (Table 2). Two trials have passed their interim analyses for safety and futility and are proceeding according to the plan. No serious adverse events or reactions have been detected thus far. The SyNAPSe trial just recently completed the randomized enrollment of subjects in Aug 2013. Although the two trials can complement each other and may provide evidence for the use of PROG in the treatment of TBI, it should be noted that in the past 40 years, it is unusual that two phase III trials using the same medicine were conducted simultaneously in the TBI field, which again emphasizes the scientist's focus on PROG.

Conclusion

A large and rapidly growing body of preclinical studies suggested that PROG has neuroprotective properties in many brain injury models. The mechanism for PROG's neuroprotection clearly does not target a single aspect of the TBI cascade, instead it works through multiple mechanisms to enhance the repair of damage to nerve cells caused by CNS injury; for example, neurotrophic, anti-inflammatory, anti-excitotoxicity, anti-lipid peroxidation and anti-apoptotic properties and so on. PROG has been proven to be safe and has shown signs of efficacy in preliminary phase II clinical trials for TBI. The two Phase III multicenter trials that will validate the safety and efficacy of PROG for the treatment of TBI are currently being conducted. PROG could become the standard of care for the treatment of TBI if clear signs of efficacy are found in these two Phase III multicenter trials.

Acknowledgements

This review was supported by grants from the Key Medi-

Table 2. Two randomized, double-blind, placebo-controlled phase III trials used to assess the efficacy and safety of progesterone in TBI patients.

	ProTECT III	SyNAPSe
Official title	Progesterone for traumatic brain injury: experimental clinical treatment	A randomized, double-blind, placebo-controlled phase 3 study to investigate the efficacy and safety of progesterone in patients with severe traumatic brain injury
Sponsor	Emory University	BHR pharma, LLC
Collaborators	31 Center of United States	PRA international and INC research
Identifier	NCT00822900	NCT01143064
Purpose	Intravenous (IV) progesterone; within 4 h of injury; a total of 96 h; moderate to severe TBI	Intravenous (IV) progesterone; within 8 h of injury; a total of 120 h; severe TBI
Primary outcome measures	GOS-E	GOS
Secondary outcome measures	DRS; Mortality	SF-36; Mortality
Estimated enrollment	1140	1180
Study start date	March 2010	June 2010
Estimated study completion date	June 2015	August 2013
Ages eligible for study	18 years and older	16 years to 70 years
Inclusion criteria	Moderate to severe TBI (GCS 12–4); blunt, closed head injury; arrival <4 h from injury	Severe TBI (GCS 8–3); at least one reactive pupil; arrival <8 h from injury
Health authority country		USA; Argentina; Austria; Belgium; China; Czech Republic; Germany; Hungary; Israel; Italy; Netherlands; Romania; Singapore; Spain; China Taiwan; United Kingdom and so on.
Website	http://clinicaltrials.gov/ct2/show/record/NCT00822900.	http://www.synapse-trial.com/

GOS, glasgow outcome scale; GOS-E, glasgow outcome scale-extended; DRS, disability rating scale; SF-36, short form (36) health survey.

cal Research platform Program of Zhejiang Province, China (2013ZDA019) and the Key Science and Technology Development Program of Hangzhou, China (20100733Q07).

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