Progesterone in the Treatment of Traumatic Brain Injury

Background

At present there is no safe and effective treatment for the acute stages of traumatic brain injury (TBI). While a number of approaches have been tried (barbiturate coma, hypothermia, mannitol, glucocorticosteroids and hyperbaric oxygen, among others), none have proven effective in clinical trials.[1] In fact, recently a major trial (CRASH) of intravenous corticosteroids in adults (n=10,008) with TBI reported a highly significant increase in death rates six months after injury (3.4% over controls) following methylprednisolone treatment.[2]

Neurosteroids and Traumatic Brain Injury

Investigating the question of whether female laboratory rats recover better than males after extensive bilateral damage to the medial frontal cortex (MFC), our laboratory hypothesised that the hormonal status of the female at the time of injury would significantly affect the extent of recovery. We found that females in the luteal stage at the time of injury showed significantly more functional recovery in spatial learning tasks and less brain swelling compared to females in the follicular phase at the time of injury.[3] When males were given post-TBI injections of progesterone (4mg/kg for 5 days), they showed decreases in cerebral oedema and improved recovery on spatial learning and sensory motor tasks and these beneficial effects could be seen even if treatment was delayed by up to 24 hours.[4,5]

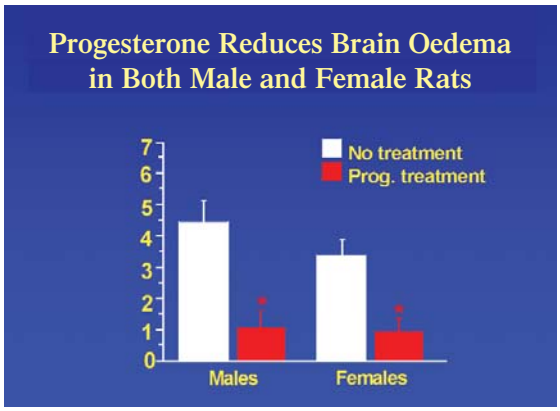

Figure 1. By 24 hours after bilateral contusions of the medial frontal cortex, post-injury progesterone significantly reduces cerebral oedema in both adult male and female rats. In a middle cerebral artery occlusion (MCAO) model of ischaemic stroke in rats, progesterone reduced tissue water content significantly.[6]

Mechanisms of Action

We now know that after brain injury, natural progesterone given to both males and females can: (1) easily cross the BBB and reduce oedema to barely measurable levels; (2) reduce lipid peroxidation and the generation of isoprostanes, which contribute to post-injury ischaemic conditions; produce metabolites which (3) decrease pro-apoptotic and increase anti-apoptotic enzymes; (4) reduce the expression of pro-inflammatory genes and their protein products; (5) reduce the area of necrotic cell death and improve behavioural outcomes; (6) protect neurons distal to the site of injury which would normally die after TBI; (7) enhance remyelination in young and aged rats with degenerative disorders; (8) produce significant sparing of cognitive, sensory and spatial learning performance in laboratory rats after bilateral injury of the MFC.[7]

Progesterone's Neuroprotective Effects

Inflammatory immune reactions. A growing literature shows that progesterone and its metabolites modulate glial cell activity to control the flow of water in and out of brain cells, and can reduce programmed cell death and the synthesis of inflammatory factors that can kill neurons hours to days after the initial injury.[9] As an anti-inflammatory agent, progesterone has been shown to reduce the response of natural killer cells as well as other known initiators of inflammation.[10]

Ischaemia. Progesterone reduces the size of infarcts caused by MCAO in rats and mice.[11] Accompanying this decrease are improvements in body weight and neurological outcomes. Progesterone appears to be effective in treating acute global ischaemia in cats,[12] where ischaemia causes a loss of 54-85% of neurons in the CA1 and CA2 subfields. After pre- and post-treatment with progesterone in female cats, neuronal loss was reduced to between 21-49%.

Functional outcomes. Damage to the frontal cortex will produce enduring bilateral sensory neglect of the forelimbs and tongue. In our studies, five days of post-injury treatment with progesterone significantly improved spatial learning and sensory performance compared to injured, untreated counterparts. Chen et al. also showed that progesterone can decrease sensory neglect and enhance sensorimotor performance after MCAO in the rat.[13]

Progesterone, Oestrogen, and MPA

Synthetic and proprietary hormones such as medroxyprogesterone acetate (MPA) may have different effects from natural progesterone in post-injury treatment. Long used in hormone therapy (HT), MPA is still widely available, but it does not mimic all the protective effects of natural progesterone, and could be a confounding variable if it were haphazardly selected for clinical testing for TBI. These differences may affect functional outcome measures, some of which can be substantially negative, such as enhancing of bone loss,[14] and preventing the reduction of atherosclerotic plaques in monkeys.[1] Recently Simoncini and colleagues[15] reported that MPA and natural progesterone have different effects on levels of LDL and HDL cholesterol. Our own preliminary data show that MPA can reduce cerebral oedema after TBI, but unlike progesterone, MPA did not result in any behavioural recovery on the tasks we used. MPA is used instead of progesterone in mouse models of sexually transmitted diseases to increase infectibility because progesterone does not have this effect. According to one recent paper, MPA increases susceptibility to genital herpes (HSV-2) ten times more than does natural progesterone.[16] Because of its ready availability, it is likely that MPA will be used again in "off-label" applications unless its differential impact on outcomes compared to natural progesterone can be clarified.

Another important concern is how progesterone and its metabolites compare to oestrogen in reducing the effects of TBI in both males and females. Unlike oestrogen, which can exacerbate brain injury, especially in animal models of ischaemic stroke,[17-20] progesterone can be given to both males and females without affecting gender and sexual functions. A recent federally supported clinical trial at Emory University using progesterone to treat TBI yielded extremely promising results (soon to be published) and found no adverse events attributable to progesterone administration.

Former Dean of the Graduate School of Arts and Sciences, **Donald Stein** is Asa G. Candler Professor of Emergency Medicine at Emory University, Atlanta, Georgia. His field of specialisation is recovery from brain injury and he has published over 300 papers, books and reviews in this area.

Correspondence to:
Donald G Stein, PhD ,
Department of Emergency Medicine, Emory University, Atlanta, Georgia, U.S.A.
Email: dstei04@emory.edu

Conclusion

The recent work on progesterone as a potential therapeutic agent in TBI has produced reliable and consistent results across species (mice, rats, cats) and in a number of injury models (TBI, stroke, spinal cord injury, soft tissue injury). Although progesterone's main effects in TBI may be to reduce cerebral oedema and stem the secondary loss of vulnerable nerve cells, it has a number of other beneficial properties. The literature indicates that progesterone is a potent anti-inflammatory, anti-apoptotic agent with some anti-oxidant properties that help to protect against the eventual breakdown of cell membranes that cause the death of neurons and glia.

In light of the recent failures of clinical trials with pharmacological agents that appear to target very selective mechanisms of injury/repair, progesterone, with its multitude of beneficial actions, may have more promise for further study and development as a safe and effective therapeutic agent in the treatment of CNS disorders.

References

1. Roberts I, Schierhout G and Alderson P (1998). *Absence of evidence for the effectiveness of five interventions routinely used in the intensive care management of severe head injury: a systematic review.* J Neurol Neurosurg Psychiatry 65:729-733.
2. Edwards P, Arango, M et al. (2005). *Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months.* Lancet 365 (2005), 1957-9.
3. Attella MJ, Nattinville A. et al. (1987). *Hormonal state affects recovery from frontal cortex lesions in adult female rats.* Behav Neural Biol 48(3):352-67.
4. Roof RL, Duvdevani R et al. (1996). *Progesterone rapidly decreases brain oedema: treatment delayed up to 24 hours is still effective.* Exp Neurol 138(2):246-51.
5. Roof RL, Stein DG (1992). *Progesterone treatment attenuates brain oedema following contusion injury in male and female rats.* Restor Neurol Neurosc 4:425-427.
6. Gibson CL and Murphy SP (2004). *Progesterone enhances functional recovery after middle cerebral artery occlusion in male mice.* J Cereb Blood Flow & Metab 24:805-13.
7. Stein DG (2005). *The Case for Progesterone, in The Future of Oestrogen and Hormone Therapy in Postmenopausal Women: What Basic Science and Clinical Studies Teach Us,* ed. M. Singh et al. New York: Ann NY Acad. Sci 1052:152-169.
8. Stein DG (2004). *Brain Trauma, Se Hormones, Neuronal Survival and Recovery of Function in Principles of Gender-Specific Medicine,* ed. Marianna Legato, Academic Press: 104-115.
9. Eldadah BA and Faden AI (2000). *Caspase pathways, neuronal apoptosis, and CNS injury.* J Neurotrauma 17(10):811-29.
10. Pettus EH, Wright DW, Stein DG, Hoffman SW (2005). *Progesterone treatment inhibits the inflammatory agents that accompany traumatic brain injury.* Brain Research 1049:112-119.
11. Jiang N, Chopp M et al. (1996). *Progesterone is neuroprotective after transient middle cerebral artery occlusion in male rats.* Brain Res 735(1):101-7.
12. Gonzalez-Vidal MD, Cervera-Gaviria M et al. (1998). *Progesterone: protective effects on the cat hippocampal neuronal damage due to acute global cerebral ischaemia.* Arch Med Res 29(2): 117-24.
13. Chen J, Chopp M et al. (1999). *Neuroprotective effects of progesterone after transient middle cerebral artery occlusion in rat.* J Neurol Sci 171(1):24-30.
14. Ishida Y and Heersche JN (2002). *Pharmacologic doses of medroxyprogesterone may cause bone loss through glucocorticoid activity: an hypothesis.* Osteoporos Int 15. 13(8):601-5.
15. Simoncini T, Mannella P et al. (2003). *In vitro effects of progesterone and progestins on vascular cells.* Steroids 68(10-13):831-6.
16. Hapgood JP, Koubovec D et al. (2004). *Not all progestins are the same: implications for usage.* Trends Pharmacol Sci 25(11):554-7.
17. Carswell HV et al. (2004). *Differential effects of 17beta-estradiol upon stroke damage in stroke prone and normotensive rats.* Cerebr Blood Flow Metab 24(3):298-304.
18. Harukuni I, Hurn PD, Crain BJ (2001). *Deleterious effect of beta-estradiol in a rat model of transient forebrain ischaemia.* Brain Res 900(1):137-42.
19. Vergouwen MD ANderson RF Meyer FB et al (2000). *Gender differences and the effects of synthetic exogenous and non-synthetic oestrogens in focal cerebral ischaemia."*Brain Res 878(1-2):88-97.
20. Theodorrsen A, Theodorrsen E (2005). *Estradiol increases brain lesions in the cortex and lateral striatumafter transient occlusion of the middle cerebral artery in rats: No effect of ischaemia on galanin in the stroke area but decreased levels in the hippocampus.* Peptides: in press.