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. 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.

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 phase 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. 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.

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.

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.

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. 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.

Ischaemia. Progesterone reduces the size of infarcts caused by MCAO in rats and mice. Accompanying this decrease are improvements in body weight and neurological outcomes. Progesterone appears to be effective in treating acute global ischaemia in cats, 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.

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, and preventing the reduction of atherosclerotic plaques in monkeys. Recently Simoncini and colleagues 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. 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, 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.
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


