

## Sex Differences with TBI

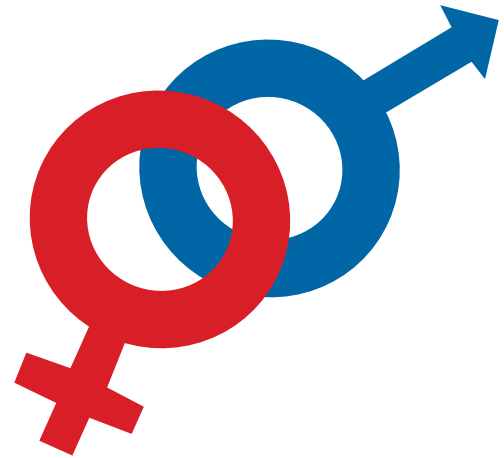
The idea that the central nervous system (CNS) can repair or recover after injury is an area of growing interest to researchers and practitioners. In the literature field this idea is called Brain Plasticity. The prevailing thought during the infancy of brain injury research in the 1960's was that once an injury occurred, CNS repair and recovery was not possible. The individual could only utilize compensatory strategies to gain function (Stein, personal communication). So researchers set out to determine the mechanisms by which function was gained post injury.

Neuroscience research in the last decade has slowly focused on identifying the mechanisms by which brain plasticity could occur. Basic research on brain injury plasticity and outcomes, of which there is relatively little compared to the sheer volume and magnitude of brain injury epidemiology in the United States, is slowly starting to emerge. The work done by these researchers has provided a rather interesting finding. Namely, that there are different functional outcomes after brain injury for females versus males. A prevailing thought has been that such differences are due to sexual dimorphism, or different structural brain anatomy (Stein, 2004).

While the jury is still out as to the direction and robustness of the results, research utilizing animal subjects has generally shown females to have better functional outcomes than males. Moreover, they found that these outcomes depended upon where the females were in their estrous cycle. When hormone levels were higher, differential outcomes between males and females are found. However, when hormone levels were lower, these differences did not exist.

One such researcher examining hormonal response in brain plasticity is Dr. Donald Stein of Emory University. Dr. Stein's current research focus is on the effects of hormones, namely progesterone and allopregnanolone, in the process of brain injury. The operative word being process. As Stein (2004) states, "Brain injury is not a unitary event, but rather a complex cascade of events that unfold over time . . . where these events can result in widespread changes in brain activity and functions." According to Stein, these events include:

- Disruption of brain integrity
- Disruption of the blood-brain barrier & bleeding
- Development of swelling within the brain
- High levels of excitatory neurotransmitter release



- Release of cytotoxic free radicals
- Release of inflammatory cytokines
- Hyperplasia, hypertrophy & migration of glial cells into the wound area
- Activation and presentation of inflammatory cells
- Release of growth inhibitory factors
- Changes in receptor activation and distribution
- Lipid peroxidation of neural membranes and demyelination
- Apoptosis and transneuronal degeneration of nerve cells.

The information to take from this list, is that these events occur throughout time, taking from minutes to years to manifest. The key then becomes to find ways to prevent the events from occurring or to find ways to reduce their effects. With all of these maladaptive events, researchers look to specific areas to target that may reduce the effects of injury or reduce the magnitude of the injury. One such area of focus is on how hormones, specifically allopregnanolone & progesterone, may affect injury. The mechanism by which they are hypothesized to affect injury is with the release of inflammatory cytokines (believed to cause swelling post injury) which in turn leads to cell death.

### Research by Stein et al.

He.J., Evans, Hoffman, Oyesiku & Stein (2004), set out to determine if allopregnanolone or progesterone can mediate (change) how cytokines (messenger RNA) affect cerebral edema (swelling). Briefly, they gave either allopregnanolone, progesterone or the solution delivery vehicle to rats in one of two conditions – rats who had surgery to create a frontal lobe contusion or rats who had “sham” surgeries with no

## Sex Differences in TBI *continued*

cerebral injury. They gave the intervention (allopregnanolone, progesterone or vehicle) at the following times: 1 hour after injury, 6 hours post injury and then daily for 5 days or so. The measures utilized to determine the effects of the intervention was the amount of messenger RNA (specifically IL-1 $\beta$ mRNA & TNF- $\beta$ mRNA) produced by the cytokines, where by higher levels would result in more swelling – lower levels in less swelling.

A summary of the results for IL-1 $\beta$  mRNA production:

1. Rats in all 3 sham surgery conditions had no differences in IL-1 $\beta$  mRNA production, regardless of whether they received allopregnanolone, progesterone or the vehicle (all  $p < .05$ ).
2. Rats in the injury conditions had higher levels of IL-1 $\beta$  mRNA production than rats in the sham surgery conditions (all  $p < .05$ ).
3. Injured rats given either allopregnanolone or progesterone had less IL-1 $\beta$  mRNA production than injured rats given only the vehicle solution ( $p < .05$ ).
4. For rats in the injury condition, those treated with allopregnanolone or progesterone had significantly ( $p < .05$ ) less IL-1 $\beta$  mRNA at 3 hours post injury. This difference was not found at 8 and 12 hours post injury.

A summary of the results for TNF- $\beta$  mRNA production:

1. Rats in all 3 sham surgery conditions had no differences in TNF- $\beta$  mRNA production, regardless of whether they received allopregnanolone, progesterone or the vehicle (all  $p < .05$ ).
2. Injured rats given either allopregnanolone or progesterone had less TNF- $\beta$  mRNA production than injured rats given only the vehicle solution ( $p < .05$ ).
3. For rats in the injury condition, those treated with allopregnanolone or progesterone had significantly less TNF- $\beta$ mRNA at 3 hours post injury ( $p < .05$ ). There was no significant difference at 8 and 12 hours post injury between rats given the vehicle solution versus rats given the allopregnanolone or progesterone.

These results point to the positive effect of allopregnanolone and progesterone on reducing TNF- $\beta$ mRNA and IL-1 $\beta$ mRNA, thereby reducing intra-cerebral swelling. However, it seems that this effect may be short lived. At 3 hours post injury, the positive effect was found. At 8 hours and 12 hours post injury, the levels of cytokines between the rats given the hormones, versus rats given only the vehicle did not exist. Overall, the results of He et.al. (2004) are promising. Continued research in this area to determine when in the injury process hormones such as allopregnanolone or progesterone reduce TNF $\beta$ mRNA and IL-1 $\beta$ mRNA and their effects will help researchers and practitioners

to know when to administer the treatment. Research then must focus on human trials to determine whether these effects replicate to human patients. ❖

*Resources:*

He,J., Evans, C.O., Hoffman, S.W., Oyesiku, N.M. and Stein, D.G. (2004). *Progesterone and Allopregnanolone Reduce Inflammatory Cytokines after Traumatic Brain Injury – Experimental Neurology* 189, pp. 404 – 412.

Stein, D.G. (2004). *Brain Trauma Sex Hormones, Neuronal Survival and Recovery of Function. Principles of Gender Specific Medicine. Volume 1, Chaper 12, pp. 104-105.*

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