## Progesterone treatment does not appear to ameliorate sensory cortical responses or behaviour in diffuse traumatic brain injury

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**Background**: Traumatic brain injury (TBI) is becoming a commonplace neurological disorder because of motor vehicle and sporting accidents in adults, and through falls in children and the elderly. It can lead to many debilitating outcomes in cognitive, motor and sensory function. A number of treatments have been proposed but only a limited number are in clinical trials. One such treatment is the administration of progesterone which has advanced to Phase II/III clinical trials, based on animal studies suggesting benefits in the form of TBI that involves focal lesions in the brain. Nothing is known of the benefits of progesterone treatment in the more common form of TBI, diffuse TBI where there is no visualizable macroscopic damage to brain tissue but axotomy and subsequent neuronal atrophy result in neurological and behaviour deficits. We examined the consequences of progesterone (P4) treatment in long-term diffuse TBI induced by an acceleration/deceleration injury method. We have previously shown that this injury method, well characterised for causing only diffuse TBI, results in long-term hyper-excitation in supra-granular sensory cortex in parallel with sensori-motor behaviour deficits, in rodents. We now examined whether regular P4 treatment would ameliorate this long-term change in neuronal response dynamics and sensori-motor behaviour.

**Methods**: Young adult rats (8-9 weeks of age), weighing between 300-320 grams, were randomly allocated to four treatment groups: (a) Sham-surgery control group treated with peanut oil vehicle (*n = 10*); (b) Brain injury group treated with peanut oil vehicle (*n = 6*); (c) Sham-surgery control group treated with P4 dissolved in vehicle (*n = 5*); (d) Brain injury group treated with P4 dissolved in vehicle (*n = 6*). Drug / vehicle treatment was done immediately after surgery and then twice more within the first 24 hours, and then weekly for 8 weeks; P4 was given at a dose of 16 mg/kg based on literature that this dose was more beneficial than higher or lower doses. Throughout the 8 week recovery period, commencing from 1 week post-surgery sensori-motor tests were conducted and compared to pre-surgery data collected from the same animals. At the end of the 8 weeks, animals were tested for behaviour one final time and then treated, using standard techniques, for terminal experiments in which electrophysiological recordings were obtained from the barrel cortex, the somatosensory cortex devoted to processing tactile input from the large face whiskers in rodents. Recordings were obtained from all layers from Layer 2 through to Layer 5, from multi-neuron clusters and from single cells extracted from those clusters, with a range of simple and naturalistic complex stimuli being delivered to the Principal Whisker of the neurons under study.

**Results and Discussion**: The outcomes were very straight-forward: P4 treatment did not affect normal sensory cortex responses (in the Sham animals) and it did not have any beneficial effect on neuronal responses in diffuse TBI. The absence of effects on neuronal responses was matched with an absence of benefit for sensori-motor behaviour that had been impaired by diffuse TBI. Clearly, interpretation of such negative findings must be subject to the caveats as to whether the dose was optimal, or whether the injection method was effective. Nevertheless, given that the dose was that shown repeatedly to be optimal in focal TBI, and the administration method was similar to that shown to have benefit for mortality in focal TBI, the present study indicates that P4 may not be uniformly beneficial in all types of TBI. We also note that the benefits of TBI reported in the literature of animal studies have generally been for mortality and for inflammatory markers post-TBI, and in the literature of human studies have been on feelings of well-being post-TBI. Thus, while we cannot exclude methodological factors from consideration as contributing to the absence of P4 benefits here, we note also that this is the only study examining P4 effects on diffuse TBI and examining neuronal responses directly.