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The Effects of Oestrogen and Progesterone on Outcome Following Experimental Traumatic Brain Injury in Rats

Christine A. O'Connor, BPsych (Hons)

Department of Pathology, School of Medicine,

University of Adelaide

July, 2004

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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ABSTRACT

A number of previous studies have suggested that female outcome following Traumatic Brain Injury (TBI) differs from male outcome, possibly because of the effects of the female gonadal hormones. How the hormones affect outcome is unclear; some reports support a protective role for the gonadal hormones whereas others suggest that there is no protective effect, and at times, even a deleterious effect. In the present study, we have used a standardised model of diffuse TBI in rats to characterise the effects of the female gonadal hormones on both female and male outcome.

Initial standardization of the impact–acceleration injury model involved characterizing the effects of injury on the different functional outcome tasks, and subsequently characterizing the effects of anaesthesia on these tasks in both male and female animals. Rate of functional improvement was generally independent of pre-injury training, with a significant effect only observed with daily testing of motor function. While weekly testing of functional outcome detected persistent deficits, daily assessment allowed for the early identification of functional deficits and the more rapid characterization of functional recovery. A differential pattern of functional recovery was apparent that was dependent upon the choice of anaesthesia for each gender, and the functional assessment task used. With respect to female outcome, isoflurane was protective, pentobarbital deleterious, while halothane had no effects on female outcome relative to males.

Ovariectomy in female animals reduced their performance on functional tests both prior to and after injury to a level similar to that observed in males. Administration of a physiological dose of either oestrogen or progesterone on a daily basis after injury

generally restored the performance of the ovariectomised females back to that of their intact female counterparts. Oestrogen and progesterone also improved motor and cognitive outcome in male animals after TBI. The female gonadal hormones had a profound effect on oedema formation after TBI in both male and female animals. In female animals, the endogenous levels of the hormones altered the temporal profile of oedema formation, with a transient delayed peak in oedema noted relative to the biphasic and sustained oedema observed in males. Exogenous administration of oestrogen or progesterone after TBI in either ovariectomised females or males attenuated the oedema formation and reduced blood–brain barrier (BBB) permeability.

At the morphological level, injured intact females demonstrated less haematoxylin and eosin dark cell change and less caspase-3 immunoreactivity in the hippocampus and cortex than injured males. When administered to either male or ovariectomised female animals, progesterone was identified as being more effective than oestrogen at reducing neuronal cell death, as identified by dark cell change and caspase-3 immunopositive staining, as well as axonal injury in white matter tracts using amyloid precursor protein.

We conclude that physiological levels of both oestrogen and progesterone improve outcome in female and male animals after TBI. This improvement may be associated with the ability of the female hormones to suppress BBB opening and oedema formation after trauma, perhaps through suppression of inflammatory pathways.