Glucocorticoid Sensitivity in Health and Disease

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Submitted 24/12/1999

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Declaration

The work presented in this thesis has been submitted to the University of Adelaide for the degree of Master of Medical Science. This work contains no material that has been accepted for the award of any other degree or diploma in any University or other tertiary institution. Some of the results of this study have been published as scientific papers.

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24/12/1999

Acknowledgments

The research undertaken as part of this degree was multidisciplinary in the broadest sense of the word. Foremost, I must acknowledge Susan March, who coordinated the project and performed the clinical interviewing of subjects. Not only a fantastic professional, but also a great person to work with.

A special thanks is extended to my supervisors Dr. Gary Wittert, and Professor McFarlane, who have provided so much assistance to me over the last two years.

I must also thank the staff of the various laboratories who allowed me to perform the assays at the core of this project. In particular the Endocrine and Metabolism unit at the Queen Elizabeth Hospital where the urinary steroid and cortisol assays were performed. Special thanks to Dr. George Phillipov without whose help these tests would have been impossible. Thanks are also extended to Bob Farrant, for his technical assistance in both the before mentioned procedures.

A thank you is also extended to Allan Bishop director of the flow cytometry laboratory at the IMVS, and co-author of one of the papers arising from this study.

Two special people also deserve mention. Firstly my fiancée Elsa, who has provided me with so much support and encouragement during a very trying period. And finally the wonderful lady who supported me throughout my life, my Grandma, who sadly passed away before seeing the completion of my studies.

Summary

It has been shown previously that chronic PTSD is associated with alterations in the activity of the hypothalamic-pituitary-adrenal axis (HPA –axis). These include diminished cortisol excretion, increased numbers of glucocorticoid receptors and increased sensitivity of the axis to low doses of dexamethasone. However, it is not known whether these alterations are fundamental to the development of the disorder, or whether they arise once the condition is established. Initially a study was conducted with six healthy controls to determine suitable dosage and administration time for dexamethasone. A second series of studies in healthy subjects was used to develop a receptor binding protocol for flow cytometry to enable the analysis of both isoforms of the glucocorticoid receptor (GR-α and GR-β). Finally, a study of HPA-axis activity in motor vehicle accident victims admitted to the Royal Adelaide Hospital was conducted to determine if aberrant HPA-axis activation in the first month following a motor vehicle accident is related to adverse psychological experiences in some individuals following a traumatic event and if the activity of the HPA-axis is related to the development of posttraumatic stress disorder in a sub-set of these individuals. Twenty male (mean age 31 $\pm$ 3 years) and seven female (mean age 45 $\pm$ 6 years) victims of a motor vehicle accident were recruited into the study. Subjects were studied within two days of the accident, one month after the accident and again six months after the accident. Female victims were more likely to develop PTSD then male victims of a motor vehicle accident ($p = 0.02$). Within two days of the accident, high scores on measures of the 'Impact of Events Scale (IES-R)', and the Stanford Acute Stress Questionnaire (SASQ)' were strongly related to the development of PTSD. Plasma

cortisol measured with 4 hours of the accident, and again two days after the accident at 08.00hrs and 16.00hrs was not different between subjects who developed PTSD and those who did not. Plasma cortisol was not related to subjects self reported level of pain. Additionally, plasma cortisol at the time of the accident was not related to scores on the IES or SASQ. 24-hour Urinary Free Cortisol the day after the accident was not related to the development of PTSD, but at one month was related to the symptoms of avoidance ($p = 0.01$) and SASQ total score ($p = 0.046$). Cortisol metabolites were measured by Gas Chromatography, but 24-hour excretion of cortisol metabolites THF, allo-THF, and THE did not differ between subjects who developed PTSD and those who did not. Dehydroepiandrosterone (DHEA) is not normally excreted into urine, however it was found in the urine of all subjects who developed PTSD the day after the accident, and at one month after the accident, but was not significantly higher than DHEA in urine of subjects who did not develop PTSD. DHEA was positively related to the total Dissociative Experiences Scale score ($p = 0.025$). A small cohort, and the large variability in the release of adrenal steroids following trauma meant that differences between diagnostic groups in the activation of the HPA-axis could not be detected. However, one month after the trauma strong relationships were found between symptoms of PTSD such as avoidance of reminders of the event, and intrusive thoughts that were related to 24-hour urinary cortisol excretion. Additionally, DHEA in urine was related to synmptoms of dissociation, which is a common symptom of PTSD. The results suggest that different neuorsteroids may mediate different components of the psychological response to a traumatic event. Dysregulation of these neuroendocrine systems may be important in the consolidation of

adverse psychological reactions to the trauma that take place in the first month after the event and may lead to the development of PTSD.