The role of the amyloid precursor protein following traumatic brain injury

Frances Corrigan BHlthSc (Hons)

Discipline of Anatomy and Pathology
School of Medical Sciences
The University of Adelaide

November 2011

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Table of Contents

Chapter 1: Introduction to traumatic brain injury and the role of the amyloid precursor protein.....1

1.1 Epidemiology.....2

1.2 Neuropathology and physiology of head injury.....3

1.2.1 Primary Injury.....4

1.2.2 Secondary Injury.....7

1.2.3 Cell Death Following TBI.....11

1.2.4 Endogenous Neuroprotective & Neurotrophic Pathways.....14

1.3 Amyloid precursor protein.....15

1.3.1 APP Isoforms.....15

1.3.2 Protein structure of APP.....16

1.3.3 Proteolytic Processing.....17

1.3.4 Functions of APP.....20

1.3.5 Factors which affect APP processing.....27

1.3.6 APP and TBI.....32

1.3.7 Therapeutic Potential of APP.....34

1.4 Experimental TBI models.....35

1.4.1 Fluid Percussion Injury.....36

1.4.2 Controlled Cortical Impact Injury.....36

1.4.3 Impact-acceleration injury model.....37

1.5 Conclusion and Aims.....38

Chapter 2: Materials and Methods.....39

2.1 Ethics.....40

2.2 Animals.....40

2.3 Experimental Procedures.....40

2.3.1 Anaesthesia.....40

2.3.2 Rat Impact-Acceleration Model of Traumatic Brain Injury.....41

2.3.2 Mouse Impact-Acceleration Model of Traumatic Brain Injury.....42

2.3.3 Mouse Controlled Cortical Impact Model of Traumatic Brain Injury....42
2.3.4 Drug Treatment....44
2.3.5 Post-surgery recovery....46
2.4 Neurological Assessment....46
2.4.1 Cognitive Testing....46
2.4.2 Motor Testing....52
2.5 Histological Analysis....54
2.5.1 Perfuse Fixation....54
2.5.2 Tissue Processing....54
2.5.3 Haematoxylin and Eosin Staining....55
2.5.4 Fluoro Jade C Staining....57
2.5.5 Immunohistochemistry....57
2.6 Caspase-3 ELISA....59
2.7 Statistical Analysis....60
Chapter 3: The neuroprotective domains of the amyloid precursor protein, in traumatic brain injury, are located in the two growth factor domains....61
3.1 Introduction....62
3.2 Experimental Design....63
3.2.1 Induction of Traumatic Brain Injury....63
3.2.2 Motor Outcome....64
3.2.3 Cognitive Outcome....64
3.2.4 Histological Analysis....65
3.2.5 Statistical Analysis....65
3.3. Results....65
3.3.1 The D1 and D6a domains of sAPPα are as effective as the full length peptide at improving motor outcome post-injury....65
3.3.2 The D1 and D6a domains of sAPPα are as effective as the full length peptide at improving cognitive outcome post-injury....66
3.3.3 The D1 and D6a domains of sAPPα are as effective as the full length peptide at reducing axonal injury post-injury....67

3.4 Discussion....69
4.2 Materials and Methods....74
4.2.1 Induction of Traumatic Brain Injury....74
4.2.2 Motor Outcome....75
4.2.3 Cognitive Outcome....75
4.2.4 Histological Analysis....76
4.2.5 Caspase- 3 ELISA....77
4.2.6 Statistical Analysis....77
4.3 Results....78
4.3.1 APP-/- Mice Have Impaired Motor Outcome following mTBI....78
4.3.2 APP-/- Mice Have Impaired Cognitive Outcome Following mTBI....79
4.3.3 APP-/- Mice Have Increased Neuronal Loss Following mTBI....80
4.3.4 APP-/- Mice Have Decreased GAP-43 Expression Following mTBI....81
4.3.5 APP-/- Mice Have Decreased Synaptophysin Levels Following mTBI....83
4.3.6 APP-/- Mice Have Increased Levels of Activated Caspase-3 Following TBI....84
4.1 Discussion....84
Chapter 5: Characterisation of the controlled cortical impact model of traumatic brain injury....88
5.1 Introduction....89
5.2 Methods....90
5.2.1 Mouse Controlled Cortical Impact Model....90
5.2.2 Motor Outcome....91
5.2.3 Cognitive Outcome....91
5.2.3 Histological Analysis....92
5.2.4 Immunohistochemistry....93
5.2.5 Statistical Analysis....94
5.3 Results....94
5.3.1 Effects of varying impact depth on motor deficits following CCI injury....94
5.3.2 Effects of varying impact depth on cognitive deficits following CCI injury....95
5.3.3 Histological characterisation of varying impact depth in the CCI model of TBI....96

5.3.4 The effect of varying impact depth on levels of GAP-43 following CCI injury 98

5.3.5 Effects of sAPPα treatment on functional outcome following moderate CCI injury 99

5.4 Discussion.....101

Chapter 6: Treatment with sAPPα is sufficient to rescue deficits in amyloid precursor protein knockout mice following focal traumatic brain injury..... 105

6.1 Introduction 106

6.2 Methods.....106

6.2.1 Mouse Controlled Cortical Impact Model.....107

6.2.2 Motor Outcome 107

6.2.3 Cognitive Outcome.....108

6.2.4 Tissue processing 108

6.2.5 Assessment of cortical tissue damage 108

6.2.6 Assessment of hippocampal damage.....109

6.2.7 Immunohistochemistry 109

6.2.8 Statistical Analysis 110

6.3 Results 110

6.3.1 sAPPα rescues motor deficits in APP-/- mice following CCI injury.....110

6.3.2 Exacerbation of cognitive deficits in APP-/- mice is prevented with sAPPα treatment 111

6.3.3 Exacerbation of cortical damage in APP-/- mice is rescued with sAPPα after CCI injury ...112

6.3.4 Increased hippocampal damage in APP-/- mice following CCI Injury is prevented with sAPPα treatment.....113

6.3.5 sAPPα treatment prevents the decrease in hippocampal levels of MAP-2 following CCI Injury seen in APP-/- mice 115

6.3.6 APP-/- Mice have decreased numbers of doublecortin positive cells following CCI injury 118

6.3.7 Knockout of APP Decreases Levels of GAP-43 Following CCI Injury 119

6.4 Discussion.....121

Chapter 7: The region encompassing the heparin binding site of the D1 domain of sAPPα is sufficient to rescue deficits in amyloid precursor protein knockout mice 126

7.1 Introduction 127

7.2 Methods.....127

7.2.1 Induction of Traumatic Brain Injury 128
7.2.2 Motor Outcome 128
7.2.3 Cognitive Outcome 129
7.2.4 Tissue processing 129
7.2.5 Assessment of brain tissue damage 129
7.2.6 Assessment of hippocampal damage 130
7.2.7 Statistical Analysis 130
7.3 Results 130
7.3.1 Motor outcome 130
7.3.2 Cognitive Outcome 131
7.3.3 Lesion Volume 132
7.3.4 Hippocampal Cell Damage 133
7.4 Discussion 134
Chapter 8: Summary and Future Directions 137
8.1 Benefit of exogenous application of sAPPα following TBI 138
8.2 The role of endogenous APP following TBI 139
8.3 Delineating the neuroprotective region within sAPPα 144
References 147

Abstract

The amyloid precursor protein (APP) is known to increase following traumatic brain injury (TBI). It has been hypothesised that this increase in APP may be deleterious to outcome due to the production of neurotoxic Aβ. Conversely, this upregulation may be beneficial as cleavage of APP via the alternative non-amyloidogenic pathway produces the soluble alpha form of APP (sAPPα), which is known to have many neuroprotective and neurotrophic functions. Indeed a previous study showed that treatment with sAPPα following a diffuse injury in rats reduced apoptotic cell death and axonal injury which corresponded with an improvement in motor outcome. However, it is not yet known whether endogenous APP plays a similar beneficial role following TBI, or which specific region within sAPPα conferred this protective activity.

In order to investigate this the effect of post-traumatic administration of various regions within sAPPα was examined following severe-impact acceleration TBI in Sprague Dawley rats. Furthermore the outcome of male C57BL6j x 129sv APP-/- mice was compared to that of APP+/+ mice following two types of traumatic brain injury; a diffuse lesion caused by a weight drop model and a focal lesion induced by a controlled cortical impact (CCI) injury.

Knockout of APP was found to worsen outcome following both a mild diffuse and moderate focal injury, with an exacerbation of motor and cognitive deficits associated with an increase in neuronal injury and an impaired reparative response. These deficits could be rescued with treatment with sAPPα, suggesting that it was lack of this APP metabolite which caused the increase in vulnerability of APP-/- mice. Furthermore initial investigations in Sprague Dawley rats found that only the domains of sAPPα that contained heparin binding sites were able to improve functional outcome and decrease axonal injury following diffuse TBI. This suggested that the neuroprotective activity of sAPPα related to its ability to bind to heparin sulphate proteoglycans. Indeed a preliminary investigation found that the peptide APP96-110, which encompassess one of the heparin binding sites within sAPPα, was sufficient to reduce functional deficits and neuronal injury in APP-/- mice.

These results demonstrate that the upregulation of APP seen following TBI is a protective response, with the benefits of sAPPα outweighing any negative effects of other APP metabolites like Aβ. The neuroprotective properties of sAPPα, may relate to its heparin binding sites, with one of these regions, APP96-110, warranting further investigation as a putative neuroprotective agent following TBI.

Declaration

This work contains no material which has been accepted for the award of any degree or diploma in any university or other tertiary institution to Frances Corrigan and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Publications and Presentations

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Corrigan F, Pham C, Vink R, Blumbergs P, Masters C, Van den Heuvel C and Cappai R. *The neuroprotective domains of the amyloid precursor protein, in traumatic brain injury, are located in the two growth factor domains.* Brain Research (2011) 1378:137-43.

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Acknowledgements

The work within this thesis would not have been possible without the support and assistance of many other people.

My primary supervisor Dr Corinna Van den Heuvel, thank you for providing me with the opportunity to undertake my PhD and for your continual support, guidance and knowledge. Throughout my PhD your door has always been open for chats about the progress of this work.

My second superivisor, Professor Robert Vink was always generous in sharing his extensive research knowledge and experience.

Associate Professor Roberto Cappai provided much of the theoretical underpinnings to the peptide studies conducted within this thesis. In particular, his extensive knowledge of the amyloid precursor protein, including its three dimensional structure and its specific active sites were crucial.

Dr Chi Pham was also critical in producing many of the proteins that were used throughout this thesis.

Dr Mark Habgood provided invaluable assistance in setting up the controlled cortical impact model, going above and beyond what was required to ensure that I had a working model. This not only included assisting in its construction, but also being willing to provide detailed and helpful answers to my many questions.

Jim Manavis, whose encyclopedic knowledge of immunohistochemistry, meant that he could assist with technical details about almost any antibody I could think to ask for. I also extend thanks to the rest of the IMVS staff, including Kathy, Serg, Sophie, Sven and Yvonne for their help throughout my studies.

The post-docs within the laboratory, Dr Stephen Helps, Dr Emma Thornton, Dr Jenna Ziebell and Dr Renee Turner provided assistance with many aspects of these studies, particularly in setting up the mouse diffuse injury model .

John Hallett for constructing many of the different functional testing apparatus used throughout this thesis including the Y Maze, Barnes Maze and ledged beams.

To my fellow PhD students, past and present who have shared part of this journey, Adam, Anna, Chris, Kate, Levon, Liz and Tim, who have made this an enjoyable experience through their help and support.

Finally, the IMVS Animal Facility, particularly Briony and Kelly for taking excellent care of my animals.

Abbreviations

Aβ	Amyloid beta
AD	Alzheimer's disease
AICD	Amyloid precursor protein intracellular domain
AIF	Apoptosis inducing factor
ANOVA	Analysis of variance
APLP	Amyloid precursor like protein
APOE	Apolipoprotein E
APP	Amyloid precursor protein
ATP	Adenosine triphosphate
BACE	Beta amyloid precursor protein cleaving enzyme
BDNF	Brain derived neurotrophic factor
CCI	Controlled cortical impact
CDK5	Cyclin dependent kinase 5
CNS	Central nervous system
CuBD	Copper binding domain
DAI	Diffuse axonal injury
DAB	3,3' Diaminobenzidine
DNA	Deoxyribonucleic acid
ER	Endoplasmic reticulum
FJC	Fluoro Jade C
FP	Fluid percussion
GFLD	Growth factor like domain
GSK-3β	glycogen synthase kinase-3β
H&E	Haematoxylin and eosin
HSPG	Heparin sulphate proteoglycans
ICV	Intracerebroventricular
IAP	Inhibitor of apoptosis
IGF-2	Insulin growth factor
IL	Interleukin
IP	Intraperitoneal
JNK3	c-Jun N-terminal kinase 3
KPI	Kunitz type protease inhibitor
LTP	Long term potentiation
NF-κB	Nuclear factor kappa B

NGF	Nerve growth factor
NT	Neurotrophin
MAP-2	Microtubule associated protein-2
MAPK	Mitogen activated protein kinase
PAT1a	Protein interacting with amyloid precursor protein tail 1a
PCD	Programmed cell death
PBS	Phosphate buffered saline
PI_3K	Phosphotidylinositol-3-kinase
PKC	Protein kinase C
PS	Presenilin
PTB	Phosphotyrosine binding
ROS	Reactive oxygen species
RGB	Red green blue
sAPPα	Serum amyloid precursor protein alpha
sAPPβ	Serum amyloid precursor protein beta
SEM	Standard error of the mean
SP	Substance P
TBI	Traumatic brain injury
TBS	Tris buffered saline
TNF-α	Tumour necrosis factor alpha

Table of Figures

Fig 1.1: Representative image of APP, demonstrating the domains within the extracellular sequence. 16
Fig 1.2: Representative image of the proteolytic processing of APP along the non-amyloidogenic and amyloidogenic pathways.....17
Fig 2.1: Injury apparatus used for induction of the impact acceleration model.....41
Fig 2.2: Evidence of axonal injury following njury 42
Fig 2.3: Representative images of the CCI device used.....43
Fig 2.4: Lesion volume (A) and degenerating neurons as detected by FJC staining within the CA region of the hippocampus (B) and dentate gyrus (C) at 5 hrs post-injury.....44
Fig 2.5: Schematic of the different peptides administered in relation to full length APP 45
Fig 2.6: Dose-response study 45
Fig 2.7: Responses elicited during shuttlebox training in Sprague Dawley rats 47
Fig 2.8: Representative photograph of the object recognition task. 48
Fig 2.9: Performance by Sprague Dawley rats on the object recognition task. 48
Fig 2.10: The Y Maze apparatus. 49
Fig 2.11: Performance by Sprague Dawley rats (A) and APP+/+ and APP-/- mice (B) on the Y Maze ..50
Fig 2.12: Representative photograph of the Barnes Maze 51
Fig 2.13: The ability of APP+/+ and APP-/- C57BL6j x 129sv mice to find an escape hole on the Barnes Maze over a 5 day training period. 52
Fig 2.14: Photograph of the rotarod device used to test motor deficits following impact-acceleration TBI in rats 53
Fig 2.15 : A diagram depicting the ledged beam 54
Fig 2.16: Representative micrograph demonstrating how the area of the cortex was outlined in order to determine the extent of cortical damage.....56
Fig 2.17: Representative micrograph of the cortex of an APP-/- mouse following the mild diffuse impact-acceleration injury. 56
Fig 3.1: Schematic of the different peptides administered within this study.....63
Fig 3.2 Motor (rotarod) scores for rats following TBI 66
Fig. 3.3: Cognitive outcome (Y Maze) on day 5 (A) and 10 (B) following injury.....67
Fig 3.4: Axonal injury within the corpus callous following TBI.....67
Fig 3.5: Representative micrographs showing the presence of a number of APP.....68
Fig 4.1: Micrograph showing the regions that were used to determine the number of healthy neurons within APP+/+ and APP-/- mice following TBI.....77

Fig 4.2: Motor outcome, as assessed on the rotarod, expressed as raw scores (A) and % pre-injury time (B).....78
Fig 4.3: Cognitive outcome as determined by escape latency (A) and ability to learn a new spatial contingency (B) on the Barnes Maze. 79
Fig 4.4: H&E labeled sections within the CA3 region of the hippocampus (40x).....80
Fig 4.5: H&E labeled sections within cortex directly underneath the impact site (40x).....81
Fig 4.6: GAP-43 immunolabeled sections within the CA1 region of the hippocampus (A-F) and cortex (G-L).....82
Fig 4.7: Colour deconvolution of synaptophysin immunohistochemistry. 83
Fig 4.8: Synaptophysin immunolabeled sections within the CA1 region of the hippocampus (40x). ...83
Fig 4.9: Levels of activated caspase-3 within the hippocampus (A) and cortex (B).....84
Fig 5.1: Representative image depicting the regions that were used to analyse GAP-43 immunohistochemistry. 94
Fig 5.2: Motor deficits, as detected on the ledged beam following graded CCI injury.....94
Fig 5.3: Cognitive outcome, as determined by the time taken to find the location of a previously learnt escape hole (A), and the ability to learn a new location for the escape hole (B). 95
Fig 5.4: Representative images taken from the region -2.5 from Bregma, demonstrating the increasing cortical and hippocampal damage that accompany increasing impact depth.....96
Fig 5.5: Representative images of MAP-2 immunohistochemistry (A-L), with colour deconvolution of the CA2 (M), CA3 (N) and dentate hilus (O) regions of the hippocampus.....97
Fig 5.6: Levels of GAP-43 within the cortex expressed as %DAB weight 98
Fig 5.7: Representative images of GAP-43 immunohistochemistry at increasing distance from the lesion site 99
Fig 5.8: Effect of treatment with sAPPα on motor (A) and cognitive outcome (B&C) following moderate CCI injury. 99
Fig 5.9: Representative images from the CA2/3 region of sham following treatment with sAPPα. ...100
Fig 6.1: Motor outcome, as assessed on the ledged beam.....110
Fig 6.2: Cognitive outcome as determined by escape latency on the Barnes Maze 112
Fig 6.3: Cortical damage, as expressed as a percentage of the uninjured left cortex. 112
Fig 6.4: Hippocampal neuronal degeneration as assessed by FJC staining at 24 hrs following injury. 114
Fig 6.5: Hippocampal neurodegeneration as assessed with H&E staining at 7 days post-injury. 115
Fig 6.6: Levels of MAP-2, as determined by colour deconvolution within the stratum radiatum layer of the CA2 region (A), the CA3 region (B) and the dentate hilus (C).....116
Fig 50: Representative images of MAP-2 immunohistochemistry.....117
Fig 6.9 : Representative images of doublecortin immunohistochemistry 118

Fig 6.8: Quantitative counts of the number of doublecortin positive cells within the dentate gyrus expressed as cells/mm. 119
Fig 6.10: Levels of GAP-43 within the cortex expressed as %DAB weight 119
Fig 6.10: Representative images of GAP-43 immunohistochemistry 120
Fig 7.1: Schematic of the different peptides administered in relation to the full length protein 128
Fig 7.2: Motor outcome as assessed by the ledged beam 131
Fig 7.3: Cognitive outcome as assessed by the ability to find a previously learnt escape hole on the Barnes Maze (A&B) and the ability to learn a new location for the escape hole over 3 trials (C&D) .132
Fig 7.4: Cortical damage was assessed using H&E staining 132
Fig 7.5: Representative images of the degree of hippocampal damage following CCI injury 133