



<http://researchspace.auckland.ac.nz>

ResearchSpace@Auckland

Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage.

<http://researchspace.auckland.ac.nz/feedback>

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the [Library Thesis Consent Form](#) and [Deposit Licence](#).

Note : Masters Theses

The digital copy of a masters thesis is as submitted for examination and contains no corrections. The print copy, usually available in the University Library, may contain corrections made by hand, which have been requested by the supervisor.

A role for growth hormone in neurorestoration and neurogenic processes in the brain

Praneeti Pathipati

**A thesis submitted in fulfilment of the
requirements for the degree of Doctor of
Philosophy in Molecular Medicine,
University of Auckland, 2010**

ABSTRACT

The cerebral growth hormone (GH) axis plays an active role following ischemic injury to the brain. Studies have shown that both GH and its receptor are endogenously upregulated in response to ischemic injury and that GH administration post-injury confers significant neuroprotection. Furthermore, there is evidence that GH has trophic effects on neural stem cells (NSCs). However, whether GH can also aid long term recovery and/or have direct effects on neurogenic processes is unclear. Both *in vivo* and *in vitro* studies were carried out to address these issues.

In vivo studies using the endothelin-1 model of focal ischemic stroke in adult rats demonstrated that a long-term unilateral continuous intracerebroventricular (ICV) infusion of GH is capable of targeting specific areas of active remodelling and neurogenic processes. Immunohistochemistry analyses revealed that ipsilaterally infused GH localised specifically to neuronal and glial progenitor cells within the ipsilateral subventricular zone, white matter tract, lesion and penumbral regions. Treatment with GH commencing 4 days after stroke accelerated recovery in one out three tests of motor function and improved spatial memory on the morris water maze test with no effect on learning. *In vitro* studies were then carried out to further elucidate the role of GH in mediating neurogenic processes that could potentially contribute to long-term recovery. Studies were also conducted using the hormone prolactin (PRL) since it is closely related to GH and has similar trophic effects on NSCs. Using NSCs with properties of neurogenic radial glia derived from fetal human forebrains, it was determined that exogenously applied GH and PRL promote the proliferation of neural stem cells in the absence of epidermal growth factor or basic fibroblast growth factor. When applied to differentiating NSC's, they both induce neuronal progenitor proliferation but only PRL has proliferative effects on glial progenitors. Both GH and PRL also promote NSC migration, particularly at higher concentrations. Interestingly, migration studies using receptor antagonists identified that both GH and PRL signal via the PRL receptor to promote migration.

In summary, these findings show that delayed treatment with GH may accelerate some aspects of functional recovery and improve spatial memory in the long-term. Furthermore, some of these beneficial effects may be mediated via its trophic effects on NSCs and thus is supportive of a role for GH in post-injury repair processes as well as developmental mechanisms in the brain.

ACKNOWLEDGEMENTS

Completing this thesis has certainly been an interesting and educational journey. Three primary supervisors, numerous funding issues and several technical issues later, I feel like I can face anything. All through this, I have been very fortunate to have the support of numerous people who helped make this thesis possible.

Dr.Mhoyra Fraser who helped me complete this journey – Your support and advice have helped me look forward and I am grateful to you for taking me on board. Dr.Arjan Scheepens who was not only my first supervisor but also a valuable mentor and friend: Thank you for initiating and seeing me through this journey, your guidance and mentorship have taught me a lot. Assoc.Prof.Christopher Williams for being an excellent director; constantly reminding me of the big picture and how to plan for the future. Dr.Thorsten Gorba for giving me a direction when I couldn't find one. You gave me skills that helped me to not only develop as a researcher but also further my thesis work. I feel deeply indebted for your financial and intellectual support. Prof.Laura Bennet who has always been much more than just a scientific advisor; thank you for providing me with physical and emotional support when I needed it the most. I will always remain extremely grateful to you for always being there for me and giving me the strength to keep going forward.

I would also like to thank several people who have extended material and technical support. Mr.Andrzej Surus for his help with the IGF1 RIAs and GH RRA, Mrs Chris Keven for SEC analyses, Mr. Eric Thorstensen for CORT Mass Spec and Urea analysis, Mr.Wing Leong for help with the surgeries, Mr.Nagarajan Kannan, Mrs Prudence Grandison, Mr.Vijay Pandey, Mr. Nethaji Muniraj and Mr.Brahmanaspati Shastri for advice and guidance with molecular work. In addition, I'm extremely grateful to Prof.Peter Lobie and Dr.Jo Perry for giving me B2036, Prof Vincent Goffin (InSerm, France) for his invaluable intellectual advice, critique and comment on my *in vitro* work along with providing me with the PRL and PRLR antagonist, Prof. Wayne Cutfield for the Genotrophin, Prof.Austin Smith and Dr.Yirui Sun (Wellcome Trust Centre for Stem Cell Research, Cambridge) for providing me with the very valuable human NSCs.

My heartfelt gratitude towards all members of what was the Baby Brain Injury group. Dr.Sumudu Ranasinghe, who was always there for any kind of support I needed and

gave me strength especially for the home run. Mrs.Larissa Christophidis who's always been a constant source of inspiration and support both as a friend and as a fellow student. Dr.Tanja Modersheim, the first out the door, for showing us the path and that it can certainly be done. Dr.Malin Gustavsson for being an awesome friend, supporter and well-wisher and Dr.Mariella Giovannangelo for being an excellent, efficient technician and a great friend.

Sincere thanks also to fellow residents of my Grad Room; Drs Sarah Hopkins, Severine Brunet-Dunand, Naeem Amiry and Nic Bougen. You guys certainly kept me sane in the most insane of periods and words can never express how much I appreciate all the fun times and fond memories. My precious friends Vinthiya, Swati, Pradeep, Megha, Anchal, Siva, Vishala, Ashwin, Akshat, and Wencke, thanks ever so much for all the fun times, hearing me out and putting up with me on strenuous days, giving me company on my late nights and for taking such good care of me when I couldn't do it myself.

I would also like to acknowledge my in-laws Mr & Mrs Veeramachaneni for all their support and encouragement and the Param family for always being there, welcoming me with open arms every single time I needed them. My husband Ram, for putting up with my emotional last phase, patiently reminding me of my capabilities and constantly supporting me from the day I know him. Finishing would have been a hell of a lot rougher without him. And lastly but most importantly, my family. Mom, dad, sis and jiju – you have always believed in me a lot more than I did myself and to say that you've supported me always would be an understatement. This would have never even been possible without you. Thank you for everything. Finally, my lil bud Rayan; everything just got better since you stepped into this world. I hope one day you will understand what your smiles, hugs and 'love yous' did for me during my PhD. I love you to bits.

TABLE OF CONTENTS

ABSTRACT.....	I
ACKNOWLEDGEMENTS	II
TABLE OF CONTENTS.....	IV
LIST OF FIGURES	VII
LIST OF TABLES	VIII
LIST OF ABBREVIATIONS	IX
1 GENERAL INTRODUCTION	2
1.1 OVERVIEW	2
1.2 STROKE	3
1.2.1 Incidence and prognosis.....	3
1.2.2 Risk Factors	4
1.2.3 Etiology and subtypes	4
1.2.4 Animal models.....	6
1.2.5 Pathophysiology of ischemic stroke	11
1.2.6 Endogenous Response to Ischemic injury.....	18
1.2.7 Brain plasticity	20
1.3 CURRENT TREATMENTS FOR ISCHEMIC STROKE.....	31
1.4 GROWTH HORMONE.....	35
1.5 PROLACTIN.....	51
1.6 AIMS.....	55
2 MATERIALS AND METHODS	58
2.1 IN VIVO STUDIES	58
2.1.1 Animals	58
2.1.2 Rat growth hormone buffer (rGH buffer).....	58
2.1.3 Stereotactic Endothelin-1 (ET1) infusion surgery.....	59
2.1.4 Overview of the in vivo studies.....	61
2.1.5 ICV Cannula and pump placement.....	62
2.1.6 Behavioural Testing.....	64
2.1.7 Blood and CSF sampling.....	66
2.1.8 Catheter status at post-mortem	66
2.1.9 Post-mortem, tissue harvestation and processing.....	67
2.1.10 Radioimmunoassay (RIA) for IGFI.....	68
2.1.11 Corticosterone high performance liquid chromatography (HPLC) coupled with mass spectrometry	69
2.1.12 Urea measurements.....	70
2.1.13 Acid Fuschin-Thionin Staining and measurement of tissue survival.....	71
2.1.14 Immunohistochemistry:.....	71
2.1.15 Quantification of GH and DCX labeling: dose response study.....	72
2.1.16 Statistics	73
2.2 IN VITRO STUDIES.....	74
2.2.1 Cell culture	74
2.2.2 Functional Assays.....	77
2.2.3 Molecular Biology	80
2.2.4 Statistics.....	85
3 CENTRAL INFUSION OF GH POST-ISCHEMIA IN THE ADULT BRAIN: BEHAVIOURAL AND ENDOCRINE EFFECTS	86
3.1 INTRODUCTION	86
3.2 RESULTS	87
3.2.1 Buffer formulation and testing	87
3.2.2 Behavioural analysis	88
3.2.3 Plasma and CSF measurements	91
3.2.4 Body and brain weights.....	92
3.3 DISCUSSION.....	94

4	CENTRAL INFUSION OF GH POST-ISCHEMIA IN THE ADULT BRAIN: REGION AND CELL-SPECIFIC TARGETING OF INFUSED GH.....	98
4.1	INTRODUCTION	98
4.2	RESULTS	99
4.2.1	<i>GH infusion after stroke may alter the tissue survival</i>	<i>99</i>
4.2.2	<i>ICV GH following injury localises to neurogenic regions and the infarct penumbral area</i>	<i>100</i>
4.2.3	<i>Quantification of GH immunoreactive cells</i>	<i>103</i>
4.2.4	<i>GH immunopositive cells double-label with DCX and GFAP</i>	<i>106</i>
4.2.5	<i>Quantification DCX staining</i>	<i>108</i>
4.3	DISCUSSION.....	111
5	DELAYED AND CHRONIC TREATMENT WITH GH AFTER STROKE MAY BE BENEFICIAL	116
5.1	INTRODUCTION	116
5.2	RESULTS	117
5.2.1	<i>Delayed onset of GH-treatment does not provide any neuroprotection.....</i>	<i>117</i>
5.2.2	<i>Delayed and chronic treatment of GH after stroke may accelerate some aspects of functional recovery.....</i>	<i>118</i>
5.2.3	<i>Delayed and chronic GH treatment improved spatial memory.....</i>	<i>121</i>
5.2.4	<i>Delivered GH was bioactive for the duration of infusion</i>	<i>122</i>
5.2.5	<i>GH treatment caused a transient increase in overall body weight but a decrease in spleen weight....</i>	<i>123</i>
5.3	DISCUSSION.....	125
6	GH HAS PROLIFERATIVE AND CHEMOATTRACTIVE EFFECTS ON NSCS IN VITRO	130
6.1	INTRODUCTION	130
6.2	RESULTS	130
6.2.1	<i>Characterisation of hNSCs.....</i>	<i>130</i>
6.2.2	<i>Physiological potency of Genotropin®.....</i>	<i>131</i>
6.2.3	<i>Basal expression of GHR, IGF1R and IGF1 but no GH or IGF2 in hNSCs.....</i>	<i>132</i>
6.2.4	<i>GH promotes the proliferation of hNSCs in the absence of EGF and bFGF</i>	<i>135</i>
6.2.5	<i>GH promotes the proliferation of neuroblasts but not glial progenitors</i>	<i>136</i>
6.2.6	<i>GH promotes the maturation of neurons but inhibits neurogenesis.....</i>	<i>137</i>
6.2.7	<i>GH promotes the migration of hNSCs</i>	<i>140</i>
6.3	DISCUSSION.....	142
7	PRL ALSO HAS PROLIFERATIVE AND CHEMOATTRACTIVE EFFECTS ON NSCS IN VITRO	149
7.1	INTRODUCTION	149
7.2	RESULTS	149
7.2.1	<i>hNSCs predominately express full length PRLR, with weak expression of the intermediate form</i>	<i>149</i>
7.2.2	<i>rhPRL promotes the proliferation of hNSCs in the absence of EGF and bFGF</i>	<i>150</i>
7.2.3	<i>rhPRL promotes the proliferation of neuroblasts and glial progenitors.....</i>	<i>151</i>
7.2.4	<i>PRL can inhibit or promote migration of hNSCs.....</i>	<i>152</i>
7.3	DISCUSSION.....	154
8	GENERAL DISCUSSION.....	158
8.1	OVERVIEW	158
8.2	MAJOR FINDINGS	159
8.2.1	<i>Central infusion of GH post ischemia in the adult brain; Behavioural and endocrine effects</i>	<i>160</i>
8.2.2	<i>Central infusion of GH post-ischemia in the adult brain; region and cell-specific targeting of infused GH</i>	<i>160</i>
8.2.3	<i>Delayed and chronic treatment with GH after stroke may be beneficial.....</i>	<i>160</i>
8.2.4	<i>GH has proliferative and chemoattractive effects on NSCs in vitro</i>	<i>161</i>
8.2.5	<i>PRL has proliferative and chemoattractive effects on NSCs in vitro</i>	<i>161</i>
8.3	IMPLICATIONS	162
8.3.1	<i>ET1 model of stroke and ICV infusion of GH.....</i>	<i>162</i>
8.3.2	<i>Effects of GH on neurogenic processes</i>	<i>164</i>
8.3.3	<i>Effects of GH on functional recovery following stroke</i>	<i>166</i>
8.3.4	<i>Effects of PRL on neurogenic processes</i>	<i>168</i>
8.3.5	<i>Use of GH and PRL in the brain: Factors to consider.....</i>	<i>171</i>
8.4	LIMITATIONS.....	172

8.5	FUTURE DIRECTIONS.....	173
8.6	SUMMARY	175
8.7	CONCLUSION	177
9	ADDENDUM.....	178
10	APPENDIX.....	179
10.1	MODIFIED BOUIN'S SOLUTION	179
10.2	0.1M PHOSPHATE BUFFERED SALINE (PBS)	179
10.3	0.01M CITRATE BUFFER	179
10.4	0.01M POTASSIUM PHOSPHATE BUFFERED SOLUTION (KPBS)	180
10.5	2, 3- AMINOPROPYLSILANE COATING FOR SLIDES	180
10.6	BUFFERS FOR IGF1 RADIOIMMUNOASSAY	180
10.6.1	<i>Buffer A: Acidic Dilution Buffer.....</i>	<i>180</i>
10.6.2	<i>Buffer B: Antibody & Tracer dilution buffer.....</i>	<i>181</i>
10.6.3	<i>Buffer C: Acidic buffer for plasma.....</i>	<i>181</i>
11	LIST OF REFERENCES	182

LIST OF FIGURES

FIGURE 1.1: OVERVIEW OF ANIMAL MODELS OF GLOBAL AND FOCAL ISCHEMIA.	7
FIGURE 1.2 GRAPH REPRESENTING THE TEMPORAL PROFILE OF THE MAJOR PATHOPHYSIOLOGICAL EVENTS UNDERLYING ACUTE FOCAL CEREBRAL ISCHEMIA.	12
FIGURE 1.3: OVERVIEW OF CELL DEATH PROCESSES THAT OCCUR IN RESPONSE TO ISCHEMIA.	14
FIGURE 1.4: SITES OF ADULT NEUROGENESIS IN THE HUMAN AND RODENT BRAINS.	25
FIGURE 1.5: GROWTH HORMONE RECEPTOR (GHR) SIGNALLING PATHWAY.	37
FIGURE 1.6: MEDIATORS OF GH RELEASE.	43
FIGURE 2.1: AN ILLUSTRATION OF THE RAT SKULL SHOWING THE TARGET SITES FOR ENDOTHELIN-1 INFUSION AND ICV CANNULA PLACEMENT. FIGURE OUTLINE DERIVED FROM [3].	60
FIGURE 2.2: TIMELINE AND SCHEMATICS OF THE DOSE REPOSE AND DELAYED TREATMENT STUDIES. THE	62
FIGURE 2.3: SDS-PAGE GEL ELECTROPHORESIS VALIDATION FOR GENOTROPIN® SOLUTION INTEGRITY.	77
FIGURE 3.1: SPECIFIC ACTIVITY OF rGH INCUBATED FOR 2 WEEKS IN THE DESIGNED rGH BUFFER.	88
FIGURE 3.2: ICV ADMINISTRATION OF GH COMMENCING IMMEDIATELY AFTER STROKE HAS NO SIGNIFICANT EFFECTS ON SENSORIMOTOR FUNCTION AT ANY OF THE DOSES STUDIED.	90
FIGURE	92
FIGURE 3.4: GH TREATMENT RESULTED IN A SIGNIFICANT RISE IN BODY WEIGHT BUT NO SIGNIFICANT CHANGE IN ANY OF THE ORGAN WEIGHTS.	93
FIGURE 4.1: LONG-TERM GH TREATMENT COMMENCING IMMEDIATELY AFTER STROKE MAY NOT CONFER NEUROPROTECTION.	100
FIGURE 4.2: GH DELIVERED VIA IMPLANTED MINIPUMPS LOCALISES TO CELLS IN KNOWN NEUROGENIC REGIONS AS WELL AS THOSE SURROUNDING THE INFARCT PENUMBRA.	103
FIGURE 4.3: QUANTIFICATION OF GH IMMUNOREACTIVE CELLS IN VEHICLE AND GH-TREATED BRAINS.	106
FIGURE 4.4: INFUSED GH LOCALISED TO DCX POSITIVE CELLS LINING BLOOD VESSELS, IN THE INFARCT PENUMBRAL REGION AS WELL AS IN AND SURROUNDING THE WMTs ON THE IPSILATERAL SIDE.	107
FIGURE 4.5: GH ALSO CO-LOCALISED TO GFAP POSITIVE CELLS.	108
FIGURE 4.6: QUANTIFICATION OF DCX IMMUNOREACTIVE CELLS.	111
FIGURE 5.1: DELAYED, LONG-TERM GH TREATMENT AFTER STROKE DID NOT ALTER LESION SIZE.	118
FIGURE 5.2: DELAYED AND LONG TERM ICV GH TREATMENT ACCELERATES MOTOR FUNCTION RECOVERY AS MEASURED BY THE FOREPAW INHIBITION TEST.	120
FIGURE 5.3: DELAYED AND LONG-TERM ICV GH TREATMENT IMPROVED SPATIAL MEMORY AS ASSESSED BY THE MORRIS WATER MAZE ...	122
FIGURE 5.4: DELIVERED GH FOR BIOACTIVE FOR THE DURATION OF INFUSION.	123
FIGURE 5.5: GH TREATMENT LEADS TO A TRANSIENT INCREASE IN BODY WEIGHT FOR THE DURATION OF INFUSION.	124
FIGURE 6.1: hNSCs ARE GROWN IN AN ADHERENT MONOLAYER AND PROPOGATED IN EGF AND bFGF.	131
FIGURE 6.2: THE PHYSIOLOGICAL POTENCY OF GENOTROPIN IS EQUIVALENT TO PITUITARY-DERIVED hGH.	132
FIGURE 6.3: hNSCs EXPRESS hGHR BUT NOT hGH.	133
FIGURE 6.4: hNSC ENDOGENOUSLY EXPRESS IGF1.	135
FIGURE 6.5: GH HAS DIFFERENTIAL EFFECTS ON THE PROLIFERATION OF hNSCs AT VARIOUS STAGES OF DIFFERENTIATION.	137
FIGURE 6.6: PRELIMINARY RESULTS SHOW rhGH HAS CONSIDERABLE EFFECTS ON THE NEURONAL DIFFERENTIATION OF hNSCs.	139
FIGURE 6.7: rhGH SIGNALS VIA THE PRLR TO PROMOTE hNSC MIGRATION.	142
FIGURE 7.1: hNSCs EXPRESS hPRLR BUT NOT hPRL.	150
FIGURE 7.2: PRL PROMOTES THE PROLIFERATION OF hNSCs AT VARIOUS STAGES OF DIFFERENTIATION.	152
FIGURE 7.3: PRL CAN SUPPRESS OR INDUCE MIGRATION OF hNSCs.	153

LIST OF TABLES

TABLE 1.1: A BRIEF DESCRIPTION OF THE IONIC AND METABOLIC CHANGES OCCURRING IN THE CORE AND THE PENUMBRA DURING ISCHEMIA	15
TABLE 2.1: PERCENTAGE OF IMPAIRMENT OF EACH MATCHED PAIR POST-STROKE.....	64
TABLE 2.2: SEQUENTIAL PROCESS OF AUTOMATED TISSUE PROCESSING.	68
TABLE 2.3: REHYDRATION OF SLIDE-MOUNTED SECTIONS PRIOR TO STAINING.	68
TABLE 2.4: FOUR-POINT SCALE USED FOR GH/DCX QUANTIFICATION.....	72
TABLE 2.5: NANODROP RESULTS OF A REPRESENTATIVE RNA SAMPLE EXTRACTED USING THE RNEASY MINI KIT	81
TABLE 2.6: LIST OF PRIMERS.	83
TABLE 2.7: LIST OF POSITIVE CONTROLS FOR EACH GENE EXAMINED USING PCR.....	84

LIST OF ABBREVIATIONS

24h – 24 hours

AC – PKA – Adenylyl cyclase – protein kinase A

ACTH – Adenocorticotrophic hormone

AMPA - α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate

APCI – Atmospheric pressure chemical ionization

β III Tubulin – Neuron-specific marker

DAB – 3,3'-Diaminobenzidine

DAPI - 4',6-diamidino-2-phenylindole, DNA stain to label nuclei

BBB – Blood brain barrier

BDNF – Brain-derived neurotrophic factor

bFGF – Basic fibroblast growth factor

BrdU - Bromodeoxyuridine

BSA – Bovine serum albumin

BV – Blood Vessels

CBF – Cerebral blood flow

CM – Conditioned medium

CNS – Central nervous system

CSF – Cerebrospinal fluid

CXCL4 – Chemokine ligand 4

DCX – Doublecortin

DCX+ - Doublecortin positive

DG – Dentate gyrus

DPX – Dibutyl phthalate (mounting medium)

E# – Embryonic day #

EGF – Epidermal growth factor

ERK – Extracellular regulated kinase

EPO - Erythropoietin

ET1 – Endothelin-1

GABA – Gamma-amino butyric acid

GAP43 – Growth-associated protein 43

GCL – Granule cell layer

GF – Growth factor

GFAP – Glial fibrillary acid protein

GH – Growth hormone
GH+ - Growth hormone positive
GGBP – Growth hormone binding protein
GHD – Growth hormone deficiency
GHR – Growth hormone receptor
GHRA – Growth hormone receptor antagonist
GHRH – Growth hormone releasing hormone
GHRS – Growth hormone receptor substrate
GLDH – Glutamate dehydrogenase
GnRH – Gonadotrophin-releasing hormone
HCl – Hydrochloric acid
hGH/PRL/NSC – Human growth hormone/prolactin/neural stem cells
hpGH – Human pituitary growth hormone
HI – Hypoxia ischemia
HPLC – High-performance liquid chromatography
ICV - Intracerebroventricular
IGF1 – Insulin-like growth factor 1
IGFBP – Insulin-like growth factor binding protein
IRS – Insulin receptor substrate
JAK-STAT- Janus activated kinase - signal transducer and activator of transcription
KPBS – Potassium phosphate buffered saline
LV – Lateral ventricle
M1 – Primary motor cortex region
MAPK – Mitogen-activated protein kinase
min - Minutes
MCA – Middle cerebral artery
MCAO – Middle cerebral artery occlusion
MWM – Morris water maze
Na₂B₄O₇ – Sodium tetraborate (borax)
NeuN – Neuronal nuclei
NGS – Normal goat serum
NMDA – N- Methyl-D-Aspartate
NSC – Neural stem cell
NZ – New Zealand
O/N – Overnight

PBS – Phosphate buffered saline
PCNA – Proliferating cell nuclear antigen
PEG – Polyethylene glycol
PFA – 4% Paraformaldehyde
PI3K – Phosphatidyl inositol triphosphate
PLC – Phospholipase C
PKC – Protein kinase C
PRL - Prolactin
PRLBP – Prolactin receptor binding protein
PRLR – Prolactin receptor
PRLRA – Prolactin receptor antagonist
RG – Radial glia
rGH/PRL/NSC – rat growth hormone/prolactin/neural stem cells
RG – Radial glia
RIA - Radioimmunoassay
RRA – Radioreceptor assay
RT – Room temperature
rtPA – recombinant tissue plasminogen activator
RT-PCR – Reverse transcriptase polymerase chain reaction
SDS PAGE - Sodium dodecyl sulfate polyacrylamide gel electrophoresis
S100 β - S100 calcium binding protein B, marker for immature astrocyte
SEC – Size-exclusion chromatography
SGZ – Sub-granular zone
SHC – Src homology containing domain
SOCS – Suppressors of cytokine signalling
SS- Somatostatin
STATs – Signal transducers and activators of transcription
SVZ – Sub-ventricular zone
WM – White matter
WMT – White matter tracts
WT – Wild-type