Medicus
Sapentiae
-
Thesis
Obsequium
Regulation of p75NTR Trafficking by Neurotrophins in the NSC-34 Motor Neuron Cell Line

Dusan Matusica
BHealth Sc, BSc (Hons)

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Centre for Neuroscience
Department of Human Physiology
Flinders University School of Medicine
Adelaide, South Australia
“The product of mental labor - science - always stands far below its value, because the labor-time necessary to reproduce it has no relation at all to the labor-time required for its original production”

Karl Marx (1818-1883)

“The most heated defenders of a science, who cannot endure the slightest sneer at it, are commonly those who have not made very much progress in it and are secretly aware of this defect”

Georg C. Lichtenberg (1742-1799)
CHAPTER 1: NEUROTROPHINS, NEUROTROPHIN RECEPTORS AND SIGNALING MECHANISMS VIA ENDOosomal TRANSPORT.........1

1.A General Introduction ...................................................................................................................... 2
  1.A.1 The Neurotrophic Hypothesis .................................................................................................. 2
  1.A.2 Diverse Roles Of Neurotrophins ............................................................................................ 3
  1.A.3 Current Progress In Neurotrophin Receptor Trafficking ....................................................... 3
  1.A.4 Neurotrophin Signaling Is Regulated By Intracellular Transport ......................................... 4
  1.A.5 Significance Of Understanding Neurotrophin Receptor Trafficking In Motor Neurons .......... 4
  1.A.6 Aims ..................................................................................................................................... 5

1.B Neurotrophins ............................................................................................................................. 6
  1.B.1 Nerve Growth Factor (NGF) .................................................................................................. 6
  1.B.2 Brain Derived Neurotrophic Factor (BDNF) And Neurotrophins 3 - 4 (NT-3-4) ................ 7
  1.B.3 Synthesis And Secretion Of Neurotrophins ........................................................................... 7

1.C Neurotrophin Receptors ............................................................................................................. 10
  1.C.1 Tyrosine Kinase Receptor Family (Trk’s) ............................................................................. 11
  1.C.2 Alternative Splicing Of Trk Receptors .................................................................................. 11
  1.C.3 Extracellular Splice Variants ................................................................................................. 13
  1.C.4 Intracellular Splice Variants .................................................................................................. 13
  1.C.5 The p75 Neurotrophin Receptor ............................................................................................ 14
  1.C.6 p75 Splice Variant And Homologue Receptors ..................................................................... 15
  1.C.7 Neurotrophin Receptors And Ligand Specificity .................................................................. 16
  1.C.8 Neurotrophin Receptor Interactors ...................................................................................... 17
  1.C.9 Ligand Promiscuity Of p75NTR ............................................................................................ 20

1.D Neurotrophin Receptor Signaling ............................................................................................... 23
  1.D.1 Tyrosine Kinase Mediated Signaling .................................................................................... 23
  1.D.2 p75NTR Signaling ................................................................................................................ 26
  1.D.3 Summary ............................................................................................................................... 29

1.E Neuronal Membrane Dynamics ................................................................................................. 30
  1.E.1 General Overview Of Endocytosis ....................................................................................... 30
  1.E.2 Macropinocytosis .................................................................................................................. 31
  1.E.3 Clathrin Mediated Endocytosis ............................................................................................. 31
  1.E.4 Caveolin Mediated Endocytosis ............................................................................................ 33
  1.E.5 Clathrin And Caveolin Independent Coated Pit Formation ................................................ 34
  1.E.6 Identification Of Endosomal Compartments ...................................................................... 34
  1.E.7 Dynamic Regulation Of Endocytosis ..................................................................................... 35
  1.E.8 Summary ............................................................................................................................... 35

1.F Endocytosis And Signaling: An Evolving Partnership ................................................................. 36
  1.F.1 Receptor Internalization Mechanisms ................................................................................... 37
  1.F.2 The Signaling Endosome Hypothesis .................................................................................... 39
  1.F.3 Signaling Endosome Components ......................................................................................... 41
  1.F.4 Alternative Models Of Retrograde Signal Propagation ........................................................ 42
  1.F.5 Unbounded Receptor Model ................................................................................................ 44
  1.F.6 Wave Propagation Model ..................................................................................................... 44
  1.F.7 Signaling Effector Model ....................................................................................................... 46
  1.F.8 Summary ............................................................................................................................... 47

1.G Motor Neuron Cell Line Clones In Research ............................................................................. 48
  1.G.1 Existing Motor Neuron Cell Lines ......................................................................................... 48
  1.G.2 Current Uses For Motor Neuron Cell Lines ........................................................................ 49
  1.G.3 NSC-34 Motor Neuronal Characteristics .......................................................................... 50
  1.G.4 Morphological Comparison Between NSC-34 Cells And Primary Motor Neuron Cultures .52

1.H Concluding Remarks .................................................................................................................... 56
CHAPTER 2: MATERIALS AND METHODS ............................................. 57

2.A Materials .................................................................................. 58
  2.A.1 Cell culture, media supplements and growth factors .................. 58
  2.A.2 Tissue culture plastic and glassware ........................................ 58
  2.A.3 Fluorescent dyes and compounds ........................................... 58
  2.A.4 Primary and secondary antibodies .......................................... 59
  2.A.5 Protein chromatography ......................................................... 63
  2.A.6 Chemical reagents, kits and compounds ................................... 63
  2.A.7 Data analysis ......................................................................... 63

2.B Methods .................................................................................... 63
  2.B.1 Mammalian cell culture ......................................................... 63
  2.B.2 Adhesion matrix for cell culture ............................................. 64
  2.B.3 Cell viability assays measuring effects of low serum media conditions .................................................. 65
  2.B.4 Cell viability assays measuring the effects of neurotrophins .................................................................. 65
  2.B.5 Retinoic acid and BDNF treatment of cell cultures ................. 65
  2.B.6 Acid phosphatase hydrolysis assay ......................................... 66
  2.B.7 Annexin-V-FITC apoptosis assay .......................................... 66
  2.B.8 Purification of antibodies ....................................................... 67
  2.B.9 Conjugation of antibodies to fluorescent compounds .............. 67
  2.B.10 Fluorescence Activated Cell Sorting (FACS) flow cytometry .... 68
  2.B.11 FACS analysis of neurotrophin binding on antibody binding ................................................................. 68
  2.B.12 Cell lysate preparation and Western Blot analysis ................. 69
  2.B.13 p75<sup>NT</sup>R internalization and pharmacological inhibition of endocytosis ......................................................... 69
  2.B.14 Immuno-endocytosis assays .................................................. 70
  2.B.15 Phase contrast microscopy ................................................... 72
  2.B.16 Confocal microscopy ........................................................... 72

CHAPTER 3: OPTIMIZATION OF NSC-34 CULTURE AND DIFFERENTIATION ................................................. 74

3.A Introduction ................................................................................. 75

3.B Culture, Maintenance and Differentiation of NSC-34 cells ............... 77
  3.B.1 Optimization of NSC-34 cell culture conditions ..........................................
  3.B.2 Analysis of cell survival rates in serum-supplemented and defined media ........................................ 80
  3.B.3 Effects of serum-supplemented and defined media on cell subtype .................................................. 80
  3.B.4 Effect of media on cell size and neurite extension in long term cultures ........................................ 82
  3.B.5 Effects of long term RA treatment in NSC-34 cells .................... 85
  3.B.6 Optimization of culture growth matrix for glass coverslips .......... 87
  3.B.7 Long-term culture in serum free media ..................................... 88

3.C Discussion .................................................................................. 90

CHAPTER 4: CHARACTERIZATION OF NSC-34 CELLS FOR THE USE IN NEUROTROPHIN RECEPTOR TRAFFICKING STUDIES ................. 95

4.A Introduction ................................................................................. 96

4.B Analysis of Cell Membrane and Cytosolic Markers ..........................................
  4.B.1 FACS and Immunofluorescence screening ..................................... 97
  4.B.2 Western Blot analysis of neurotrophin receptors and endogenously expressed neurotrophins ................................................. 98
  4.B.3 Effects of Culture Media on Neurotrophin Receptor Expression ........................................................................ 104

4.C Physiological responses of NSC-34 cells to neurotrophins .................... 106
  4.C.1 Effect of exogenous neurotrophins on NSC-34 cells ....................... 106
  4.C.2 Analysis of neurotrophin induced cell death ................................ 108
4.D. Neurotrophin receptor interactions with receptor specific antibodies
4.D.1 Effects of neurotrophins on binding of p75NTR, TrkB, TrkC and Sortilin
4.D.2 Effects of p75NTR antibodies on NGF induced apoptosis
4.D.3 Time-lapse internalization of p75NTR
4.D.4 Time-lapse internalization of TrkB
4.D.5 Effects of k252a on neurotrophin receptor internalization

4.E Discussion

CHAPTER 5: EXOGENOUS NEUROTROPHINS REGULATE THE SUBCELLULAR FATE OF p75NTR

5.A Introduction

5.B Internalization of p75NTR in the presence of neurotrophins
5.B.1 p75NTR internalization rates are altered in the presence of exogenous neurotrophins.
5.B.2 p75NTR associates with GT1b on the cell membrane but is internalized via clathrin mediated endocytosis.
5.B.3 p75NTR associates with clathrin HC and transferrin positive endocytic carriers.
5.B.4 Inhibition of clathrin-mediated endocytosis prevents p75NTR internalization in the presence of BDNF and NT-4, but not NGF and NT-3.

5.C p75NTR endosomal trafficking dynamics
5.C.1 NGF and NT-3, but not BDNF and NT-4 decrease lysosomal targeting of p75NTR.
5.C.2 p75NTR enrichment of EEA-1 positive endosomes is dependent on NGF and NT-3, but not BDNF and NT-4.
5.C.3 NGF and NT-3 reduce p75NTR recycling to the plasma membrane.

5.D Discussion

CHAPTER 6: DISCUSSION AND FUTURE PROSPECTS

6.A Discussion
6.A.1 Neurotrophin Biology
6.A.2 The NSC-34 cell line as a motor neuron model
6.A.3 Neurotrophin receptor trafficking
6.A.4 Is there a distinct p75NTR signaling endosome?

6.B Future Prospects

APPENDIX

Appendix 1: Mapping of MLR antibodies binding domains to p75NTR.

REFERENCES:
LIST OF TABLES

TABLE 1 - NEURONAL PROPERTIES AND MARKERS OF NSC-34 CELL LINE ........................................ 54
TABLE 1 - NEURONAL PROPERTIES AND MARKERS OF NSC-34 CELL LINE ........................................ 55
TABLE 2.1 - LIST OF PRIMARY ANTIBODIES AND WORKING DILUTIONS ........................................ 60
TABLE 2.2 - LIST OF PRIMARY ANTIBODIES AND WORKING DILUTIONS ........................................ 61
TABLE 3 - LIST OF FLUORESCENT SECONDARY ANTIBODIES AND WORKING DILUTIONS .......................................................... 62
TABLE 4 - LIST OF HRP AND ALKALINE PHOSPHATASE CONJUGATED SECONDARY ANTIBODIES AND WORKING DILUTIONS .............................. 62
TABLE 5 - PMT GATE SETTINGS FOR CELL MEMBRANE AND NUCLEAR MARKER EMISSION .......................................................... 73
TABLE 6 - PMT GATE SETTINGS FOR FLUID-PHASE MARKER EMISSION ........................................ 73

TABLE OF FIGURES

FIGURE 1.1 - THE PROCESSED AND UNPROCESSED MONOMERIC FORM OF NEUROTROPHINS .......................................................... 9
FIGURE 1.2 - SCHEMATIC REPRESENTATION OF TRK AND P75NTR STRUCTURAL ISOFORMS .......................................................... 12
FIGURE 1.3 - NEUROTROPHIN INTERACTIONS WITH THEIR RECEPTORS .................................................. 18
FIGURE 1.4 - SCHEMATIC REPRESENTATION OF RECEPTOR INTERACTORS AND P75NTR ALTERNATE LIGANDS .......................................................... 22
FIGURE 1.5 - TRK RECEPTOR-MEDIATED SIGNALING PATHWAYS .................................................. 24
FIGURE 1.6 - P75NTR-MEDIATED SIGNALING PATHWAYS .................................................. 27
FIGURE 1.7 - BIOSYNTHETIC AND RECYCLING ROUTES AND THE ENDOosomal NETWORK .......................................................... 32
FIGURE 1.8 - NEUROTROPHIN RECEPTOR INTERNALIZATION .......................................................... 38
FIGURE 1.9 - THE RETROGRADE "SIGNALLING ENDOsomE" MECHANISM .................................................. 40
FIGURE 1.10 - THE SIGNALLING ENDOsome .......................................................... 43
FIGURE 1.11 - ALTERNATIVE MODELS OF RETROGRADE NEUROTROPHIN SIGNALING .......................................................... 45
FIGURE 1.12 - MORPHOLOGICAL COMPARISON BETWEEN CULTURED PRIMARY EMBRYONIC MOTOR NEURONS AND NSC-34 CELLS .......................................................... 53
FIGURE 2.1 - SCHEMATIC REPRESENTATION OF APOPTOSIS ASSAY TIMELINE .................................................. 67
FIGURE 2.2 - SCHEMATIC REPRESENTATION OF LIVE AND FIXED IMMUNOENDOCYTOSIS ASSAY TIME LINE .......................................................... 71
FIGURE 3.1 - GROWTH MEDIA ASSOCIATED MORPHOLOGICAL CHARACTERISTICS OF NSC-34 CELLS .......................................................... 79
FIGURE 3.2 - EFFECTS OF SERUM SUPPLEMENTED AND DEFINED MEDIA ON CELL SURVIVAL .......................................................... 81
FIGURE 3.3 - ANALYSIS OF NSC-34 CELL SUBTYPES IN SERUM SUPPLEMENTED AND DEFINED MEDIA .......................................................... 83
FIGURE 3.4 - CELL BODY SIZE AND NEURITE PROCESS QUANTIFICATION .......................................................... 84
FIGURE 3.5 - RETINOIC ACID INDUCED NSC-34 DIFFERENTIATION .......................................................... 86
FIGURE 3.6 - OPTIMISATION OF CULTURE SUBSTRATE MATRIX FOR GLASS COVERSLEPS .......................................................... 89
FIGURE 3.7 - LONG-TERM CULTURE OF DIFFERENTIATED NSC-34 CELLS .......................................................... 91
FIGURE 4.1 - FACS SCREENING OF NSC-34 CELLS .......................................................... 99
FIGURE 4.2 - IMMUNOFLUORESCENCE OF MOTONEURONAL MARKERS EXPRESSED BY NSC-34 CELLS .......................................................... 100
FIGURE 4.3 - WESTERN BLOT ANALYSIS OF NEUROTROPHIN RECEPTORS AND INTRACELLULAR TRANSPORT PROTEINS .......................................................... 101

iv
Abstract

Neurotrophins are a family of growth factors necessary for the development and maintenance of the nervous system. They produce their effects through receptor mediated signaling mechanisms that are highly regulated by sophisticated intracellular transport networks. The impairment of intracellular trafficking of neurotrophins in motor neurons has been identified as one possible factor in the development of motor neuron diseases, but remains inadequately studied. Aided by advances in imaging technology and the development of more powerful and sensitive detection tools for in-vitro studies, the dynamics of intracellular transport of neurotrophins are beginning to be unraveled. However, a primary limiting factor in the study of neurotrophin-transport dynamics in motor neurons has been the lack of alternative and easily available in-vitro systems able to substitute the often difficult and costly primary motor neuron cultures.

The aim of this project was to develop a suitable motor neuron model using the NSC-34 cell line for the study of receptor mediated trafficking events through endosomal transport pathways. Successful evaluation and characterization of NSC-34 cells for motor neuron specific markers would result in the investigation of the p75 neurotrophin receptor (p75NTR) trafficking pathways in the presence of exogenous neurotrophins, with a variety of confocal imaging techniques.

Chapter 3 describes the optimisation of NSC-34 cell culture conditions through media modification and the development of a suitable growth substrate matrix, which significantly improved cell adhesion, differentiation and the ability to culture the cells for extended time periods in serum free conditions. Quantitative measurements of cell proliferation, culture viability, cell-body size and neurite length are described to highlight the increased value of the cell line for long-term culture and experiments examining a broad range of issues relevant to motor neurons.
In Chapter 4, multiple experimental approaches were used to extensively
screen the NSC-34 cell line for the presence of motor neuron-specific markers,
neurotrophin receptors and proteins involved in regulation of endosomal
transport. This characterization established the presence of a developing motor
neuron-like neurotrophin receptor profile (p75NTR, TrkB and TrkC), a genetic
marker of developing motor neurons, cholinergic markers, proteins regulating
transport within the endosomal pathway, and additional proteins previously
shown to directly interact with neurotrophin receptors, including sortilin, and the
lipid raft associated ganglioside GT1b. Furthermore, evidence is provided that
NSC-34 cells undergo apoptosis in response to exogenous nerve growth factor
(NGF) or neurotrophin-3 (NT-3), but not brain derived neurotrophic factor
(BDNF) or neurotrophin-4 (NT-4). In addition characterization of mouse specific
p75NTR antibodies is presented to establish their suitability for internalization
studies without altering the binding of exogenous neurotrophins to the receptor.

Subsequent confocal microscopy examination focusing on p75NTR
trafficking in Chapter 5 revealed that internalization and intracellular transport of
this receptor is regulated by exogenous neurotrophins at the cell surface where
ligand binding and internalization occur, and in endosomal compartments where
the bulk of receptors and ligands are targeted to their specific destinations.
Evidence is provided showing that p75NTR internalization is altered in the
presence of NGF, NT-3, or NT-4, but not BDNF, and the receptor is diverted into
non-clathrin mediated endosomal pathways in response to NGF but not BDNF.
Immunofluorescence confocal microscopy suggests that p75NTR recycles to the
plasma membrane in a Rab4 GTPase dependent manner in the absence of
neurotrophins. Addition of neurotrophins diverted p75NTR from the recycling
Rab4 positive pathway, into EEA-1 positive sorting endosomes in the presence of
NGF or NT-3, or lysosomal degradation in the presence of BDNF or NT-4.
This study clearly demonstrates the suitability of the NSC-34 cell line as an alternate in-vitro system for the study of motor neuron biology, particularly the study of neurotrophin receptor trafficking. Taken together the results represented in this study suggest for the first time, that the fate of the p75NTR receptor depends on which neurotrophin is bound. These findings have important implications for understanding the dynamic mechanisms of action of p75NTR in normal neuronal function, and may also offer further insight into the potential role of neurotrophins in the treatment of neurodegenerative diseases.
Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge or belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Dusan Matusica
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Publications and manuscripts arising from this research


MATUSICA, D., ROGERS, M. L. & RUSH, R. A. (Submitted) NSC-34 cells: enhanced differentiation and adhesion increases value as a motor neuron cell line.

MATUSICA, D., ROGERS, M. L. & RUSH, R. A. (Submitted) NGF and NT-3, but not other neurotrophins, prevent trafficking of p75NTR to lysosomes in NSC-34 cells.
**LIST OF ABBREVIATIONS**

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<tbody>
<tr>
<td>Ab</td>
<td>Antibody</td>
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<tr>
<td>Akt</td>
<td>Serine/threonine kinase / protein kinase B</td>
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<tr>
<td>BDNF</td>
<td>Brain derived neurotrophic factor</td>
</tr>
<tr>
<td>BSA</td>
<td>Bovine serum albumin</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>DMEM</td>
<td>Dulbecco’s modified Eagle’s medium</td>
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<tr>
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<td>DRG</td>
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