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The Effect of AAV_{1/2} Mediated Delivery of Brain-Derived Neurotrophic Factor and Fibroblast Growth Factor-2 on Adult Rodent Neurogenesis

Rebecca Ann Henry

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Faculty of Medical and Health Sciences, The University of Auckland, 2006
The University of Auckland

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Abstract

Neurogenesis is the process by which functionally integrated neurons are generated from progenitor cells. In the adult mammalian brain two sites of high density cell division have been identified that contain neural progenitor cells retaining the ability to generate new neurons: the subgranular zone of the hippocampus (SGZ) and the subventricular zone (SVZ) lining the lateral ventricles in the forebrain. Several studies have suggested that SVZ neural progenitor cells in the adult brain can migrate into regions other than the olfactory bulb after either administration of growth factors, induction of neuronal cell loss or injury. Brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF-2) play major roles in regulating the survival and fate of progenitor cells in the adult mammalian brain. To determine the effect of BDNF or FGF-2 on neurogenesis in the injured adult brain, BDNF or FGF-2 were over-expressed in the subventricular zone (SVZ) via recombinant adeno-associated virus (AAV1/2) delivery and newly generated cells were identified using bromodeoxyuridine (BrdU; 150mg/kg intraperitoneal) labelling. Selective striatal cell loss was induced in a subgroup of rats by unilateral striatal injection of the excitotoxin quinolinic acid (QA) 21 days after AAV1/2 injection and 24 hours prior to BrdU labeling. The results of this thesis demonstrate that BDNF augments the recruitment, neuronal differentiation and survival of progenitor cells in both neurogenic and non-neurogenic regions of the unlesioned or QA lesioned brain. BDNF also appears to contribute to the persistence of newly generated neurons in the QA lesioned striatum. Our results provide the first evidence demonstrating the neurogenic effect of BDNF on compensatory striatal neurogenesis in the injured adult brain and suggest that enhanced BDNF expression may be a viable strategy for inducing or augmenting endogenous neural progenitor cell neurogenesis. Unlike the effect of BDNF, FGF-2 appears to have no effect on proliferation and/or survival of neural progenitor cells in either the normal or damaged brain. FGF-2 appears to be unable to act as a positive mediator of SVZ progenitor cell proliferation and neurogenesis in this study. However, FGF-2 may be having an inhibitory effect on progenitor cell differentiation. The negative result of the FGF-2 study may be of major significance in indicating the potential requirement of additional factors interacting with FGF-2 to influence neurogenesis. The results from the FGF-2 study contribute to the research field in highlighting the complexity of the mammalian neurogenic process. This thesis highlights the need for further investigation into multiple factor interactions, tighter regulation of the transgenic protein expression from the AAV1/2 delivery vector or alternative progenitor cell labelling paradigms. However, it does show that if neurogenesis can be induced or augmented exogenously, neural progenitor cells may provide a substrate for repair in the adult brain and dramatically change therapeutic approaches towards the treatment of neurodegenerative diseases.
For Anthony

Without you, I would never have started or finished.
Acknowledgements

I would never have got this thesis finished (or started) without the help and support of a lot of people.

Firstly, I would like to thank my primary supervisor Dr. Bronwen Connor, who took me on even though I knew nothing about the brain except that I was pretty sure I had one and I knew how to use it! I have learnt so much working in your lab Bronwen and you’ve given me every opportunity to grow and learn, so thank you.

I would also like to thank my co-supervisor Prof. Richard Faull for seeing my potential and introducing me to Bronwen to get the ball rolling and for reading various abstracts, manuscript drafts and funding applications. Thank you also to all the members of the During/Young Lab for giving me space to work in when I first started, for gifting us the luciferase control plasmid and all the advice about packaging.

A very special thank you goes to all the members (past and present) of the Connor Lab. You guys made all the hours doing surgeries, perfusions, immuno, microscope work and all those other mind numbing jobs so much easier to bear. I also have to thank everyone in the Pharmacology Department and the wider HRC and Auckland Neuroscience Network community. Everyone I have been involved with has made my time enjoyable and oh so entertaining. Thanks especially to all those people who frequented the tearoom for making lunch time something to really look forward to everyday and always making me laugh (often at myself!)

I don’t know what I would have done without the love and support of all my friends and family. Thank you some much Matt and Marie for giving me somewhere to live when I first moved up to the big smoke and for looking after me while I found my feet. And thank you Mum and Dad for worrying about me and making sure I always looked after myself and for trying to understand what it I do. To all my friends new and old; I don't know what I would have done without you keeping me sane and knowing when not to ask how 'it' was going.

Finally to Anton, I don’t know what was, worse rats or flies?! But, you believed in me even when I didn’t believe in myself and have kept me going throughout all of this. You encouraged me to start and reminded me that I was good enough to keep going and finish. Thank you for doing this PhD with me.
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</tr>
<tr>
<td>BSA</td>
<td>Bovine serum albumin</td>
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