INSULIN-LIKE GROWTH FACTOR-I (IGF-I): ROLE AND APPLICATION IN INTESTINAL DISEASE

Gordon Stanley Howarth B Sc (Hons)

A thesis submitted for the degree of Doctor of Philosophy

Child Health Research Institute and Cooperative Research Centre for Tissue Growth & Repair, Women's and Children's Hospital, Adelaide, South Australia

and

Department of Physiology, University of Adelaide, Adelaide, South Australia

November 2001

TABLE OF CONTENTS

ABSTRACT	.....	**viii**
DECLARATION OF ORIGINALITY AND AUTHORSHIP	.....	**x**
ACKNOWLEDGMENTS	.....	**xi**
INTRODUCTION	.....	**1**
LITERATURE REVIEW	.....	**2**
1. Introduction	.....	**2**
2. The gastrointestinal tract	.....	**3**
2.1 **Structure and function of the gastrointestinal tract**	.....	**3**
2.2 **Gastrointestinal dysfunction**	.....	**7**
2.2.1 **Reduced bowel mass**	.....	**7**
2.2.2 **Atrophy**	.....	**9**
2.2.3 **Ulceration**	.....	**10**
2.2.4 **Dysmotility**	.....	**11**
2.3 **Conventional treatment strategies**	.....	**11**

3. Growth factors and the gastrointestinal tract **13**

3.1 **Endogenous growth factors** **14**

3.2 **Epidermal growth factor family (SP1,SP2, SP3, SP4)**..... **14**

3.2.1 **EGF** **16**

3.2.2 **Transforming growth factor-α (TGF-α)** **17**

3.2.3 **Betacellulin** **19**

3.3 **Transforming growth factor-β (SP3)** **20**

3.4 **Hepatocyte growth factor (SP5)** **22**

3.5 **Keratinocyte growth factor** **22**

3.6 **Trefoil peptides (SP6)** **23**

3.7 **Glucagon-like peptide-2** **24**

4. Insulin-like growth factor-I and the gastrointestinal tract **26**

4.1 **The IGF system** **27**

4.1.1 **IGF ligands and receptors** **27**

4.1.2 **Regulation of IGF bioactivity** **29**

4.1.3 **The GH/IGF-I axis** **31**

4.1.4 **IGF-I and cell kinetics** **34**

4.1.5 **Analogues of IGF-I** **36**

4.2 **Endogenous IGF-I and the gastrointestinal tract** **39**

4.3 **Exogenous IGF-I and the gastrointestinal tract** **39**

4.3.1 **Exogenous IGF-I and the adult gut (SP7–11)** **40**

4.3.2 **Exogenous IGF-I and the neonatal gut** **42**

5. IGF-I and bowel disease 43

5.1 **IGF-I and catabolic conditions (SP12, SP13)** 44

5.2 **IGF-I and radiation enteritis (PP1, SP14, SP15)** 46

5.3 **IGF-I and chemotherapy-induced mucositis (PP2)** 49

5.4 **IGF-I and inflammatory bowel disease (IBD) (PP3)** 51

6. IGF-I and bowel cancer 54

6.1 **IBD and colon cancer** 56

6.2 **IGF-I and IBD-related colon cancer (PP4)** 57

7. Clinical applications of IGF-I 58

7.1 **IGF-I and the short bowel syndrome (SP12)** 58

7.2 **Side-effects of IGF-I treatment** 62

8. Treatment of gut disease with bioactive formulations 64

8.1 **Milk and colostrum** 65

8.2 **Whey-derived growth factor extract (WGFE)** 67

8.3 **WGFE and gastrointestinal disease** 67

8.3.1 **WGFE and mucositis (PP5, PP6, SP16)** 68

8.3.2 **WGFE and IBD (SP17)** 72

DISCUSSION and CONCLUSIONS (SP18) 74

ABSTRACT

Insulin-like growth factor-I (IGF-I) : role and application in intestinal disease.
Gordon S Howarth. Child Health Research Institute, CRC for Tissue Growth & Repair and Department of Physiology, University of Adelaide. PhD Thesis. November, 2001.

The principal (**PP**) and supporting (SP) peer-reviewed publications contained within this thesis describe studies which have contributed significantly to the understanding of growth factor functionality in the processes of protection, growth and repair in the diseased or damaged gastrointestinal tract. I am first author on the principal publications and co-author on the supporting publications. My personal contributions to each of these studies [described more comprehensively in Appendices A (**PP**) and B (SP)], ranged from the initial development of hypotheses and the design and execution of experiments, through to the preparation of manuscripts for publication. These studies have extended our understanding of the mechanism of action, and the therapeutic potential, of insulin-like growth factor-I (IGF-I) (**PP1-PP5**) and of several other growth factors, in the normal and damaged gastrointestinal tract. The latter include epidermal growth factor (SP1,SP2), transforming growth factors-α and -β (SP3), betacellulin (SP4), hepatocyte growth factor (SP5) and trefoil peptides (SP6).

Initial observations that IGF-I possessed trophic selectivity for the gut (SP7-SP11) were extended through the use of IGF-I analogues with altered bioavailability which demonstrated IGF binding protein modulation of IGF activities on gut growth and repair. In addition, a number of gastrointestinal conditions for which IGF-I therapy may be effective have been identified from experimental studies utilising animal models of gastrointestinal disease in which IGF-I promotes bowel re-growth. Early indications of IGF-I efficacy in gastrointestinal repair were derived from studies in catabolic states, including bowel resection (SP12) and glucocorticoid-induced villous atrophy (SP13).

Subsequent studies, however, have suggested a primary therapeutic role for IGF-I during the repair phase, immediately following acute gastrointestinal damage, including the recovery phase of radiation enteritis (**PP1**,SP14,SP15), chemotherapy-induced intestinal mucositis (**PP2**) and acute episodes of colitis (**PP3**). As a result of these studies, IGF-I has recently been accorded Orphan Drug status for the treatment of the short bowel syndrome and final planning for a clinical trial is currently in progress. In addition to identifying candidate target conditions in gastrointestinal disease or damage for therapeutic intervention by IGF-I, these studies have also contributed to knowledge on the possible influence of IGF-I treatment on cancer risk. In a study investigating the effects of chronic IGF-I administration in a model of inflammatory bowel disease with neoplastic predisposition (**PP4**), IGF-I did not affect the progression of bowel dysplasia. In more recent studies, therapeutic potential of enterally-administered bioactive formulations comprising many concentrated growth factors including IGF-I has been investigated. One such formulation is the bovine-sourced whey-derived growth factor extract (WGFE), which has demonstrated efficacy in promotion of gut repair in models of chemotherapy-induced intestinal mucositis (**PP5**,SP16) and colitis (SP17). WGFE has since been patented as a potential treatment for oral mucositis following radiotherapy or chemotherapy (**PP6**) and a Phase II clinical trial is currently underway.

The work contained within this thesis has extended our understanding of growth factors, particularly of IGF-I, in gut growth and repair in addition to the physiological role and hence, therapeutic potential, of a range of growth factors in gastrointestinal disease. Future evaluation of the application of growth factors to combat gastrointestinal disorders could focus on functional outcomes such as effects on intestinal absorption. In addition, the efficacy of growth factor analogues with increased bioactivity, possibly incorporated into enterally-administered growth factor formulations, either enriched in, or depleted of, certain specific growth factors, could be investigated as a novel treatment strategy for diseases of the gastrointestinal tract.