GLUCOSE METABOLISM IN THE CRITICALLY ILL

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by

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ABSTRACT

Hyperglycaemia occurs frequently in the critically ill, even in those without a history of diabetes, and is associated with adverse outcomes. While the gastrointestinal tract is pivotal in the regulation of glucose metabolism in health and diabetes, this relationship had not been explored in the critically ill. The focus of this thesis is glucose metabolism in the critically ill, with a particular emphasis on the role of the gastrointestinal tract in modulating blood glucose concentrations. The work submitted for this thesis comprises two studies validating methodologies and eight subsequent studies.

In health, hormones secreted from the small intestine have the capacity to modulate gastric emptying. Studies were designed to further evaluate hormonal mechanisms underlying gastric emptying. The student established that in health endogenous glucagon-like peptide-1 (GLP-1) slows gastric emptying and glucose absorption, thereby attenuating postprandial glycaemia *(chapter 4.2)*.

In the critically ill, glucose absorption was quantified following small intestinal administration, and it was observed that absorption was markedly impaired when compared to health *(chapter 5.2)*. Despite the reduction in glucose absorption, postprandial glycaemic excursions were sustained for longer in the critically ill, attesting to the marked disturbance in glucose disposal in this group.

The current management of 'feed-intolerance' in the critically ill involves delivery of nutrient via a postpyloric catheter, or administration of a gastrokinetic drug during intragastric feeding. When comparing postpyloric and intragastric delivery of nutrient the student observed that the former route is associated with more rapid glucose absorption and exaggerated 'early' glycaemic excursions, but no clear increase in overall absorption *(chapter 5.3)*. In clinical practice postpyloric delivery of nutrient is recommended because this technique can increase delivery of nutrient, which is assumed to equate to an improvement in nutritional outcomes. However, the observations from the student's previous study challenge this premise. A further study showed that a single dose of erythromycin acutely increased small intestinal glucose

absorption, but possibly reduced lipid absorption and slowed small intestinal transit *(chapter 5.4)*.

A series of studies examined the potential for a novel method to glucose-lowering in the critically ill by administering GLP-1 in pharmacological doses. It was shown that GLP-1 markedly attenuated the glycaemic response to small intestinal feeding in non-diabetic critically ill patients *(chapter 6.2)*, but that this effect appeared to be more modest in those patients with pre-existing diabetes *(chapter 6.3)*. The mechanisms underlying the glucose-lowering effects of exogenous GLP-1 in the former group were then studied in more detail *(chapter 6.4)*. In the critically ill pharmacological doses of GLP-1 have insulinotropic and glucagonostatic properties. Furthermore, exogenous GLP-1 has the capacity to reduce the rate of carbohydrate absorption as a result of slowing gastric emptying when the latter 'normal', but not when it is delayed.

In summary, the studies described in this thesis have yielded a number of novel and important insights. These include the mechanisms underlying glucose absorption in health, quantification of glucose absorption in the critically ill, and the use of a potentially novel therapy (GLP-1) to regulate glycaemia in the critically ill.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution 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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Adam Matthew Deane
27 February 2012

PUBLICATIONS

A proportion of the work presented in this thesis has also been published in peer-reviewed journals. The section of the thesis where this published work is included is provided below:

Deane AM, Chapman MJ, Fraser RJ, Bryant LK, Burgstad C and Nguyen NQ. Mechanisms underlying feed intolerance in the critically ill: implications for treatment. *World Journal of Gastroenterology* 2007 Aug; 13(29):3909-17. Relevant section in this thesis: Chapter 1.

Deane AM, Fraser RJ, Chapman MJ. Prokinetic drugs for feed intolerance in critical illness: Current and potential future therapies. *Critical Care and Resuscitation* 2009 Jun; 11(2):132-43. Relevant section in this thesis: Chapter 1.

Deane AM, Chapman MJ, Fraser RJL, Horowitz M. Bench-to-bedside review: The gut as an endocrine organ in the critically ill. *Critical Care* 2010 Sep; 14(5):228. Relevant section in this thesis: Chapter 1 and 2.

Deane AM, Chapman MJ, Horowitz M. The therapeutic potential of a venomous lizard: The use of GLP-1 analogues in the critically ill. *Critical Care* 2010 Oct; 14(5):1004. Relevant section in this thesis: Chapter 2.

Deane AM, Fraser RJL, Young R, O'Connor S, Foreman B, Chapman MJ. An effective bedside technique for the post-pyloric placement of feeding catheters. *Critical Care and Resuscitation* 2009 Sept; 11(3): 180-3. Relevant section in this thesis: Chapter 3.

Deane AM, Zaknic AV, Summers M, J Chapman MJ, Lang K, Ritz M, Davidson G, Horowitz M, Fraser RJL. Intrasubject variability of gastric emptying in the critically ill using a stable isotope breath test. *Clinical Nutrition* 2010 Oct; 29(5):682-86. Relevant section in this thesis: Chapter 3.

Deane AM, Nguyen NQ, Steven JE, Fraser RJ, Holloway RH, Burgstad C, Besanko LK, Jones KL, Rayner CK, Chapman MJ, Horowitz M. Endogenous glucagon-like peptide-1 slows gastric emptying in healthy subjects attenuating postprandial glycemia. *Journal of Clinical Endocrinology and Metabolism* 2010 Jan; 95(1):215-21. Relevant section in this thesis: Chapter 4.

Deane AM, Summers MJ, Zaknic AV, Chapman MJ, Bartolomeo AE, Bellon M, Maddox A, Russo A, Horowitz M. Glucose absorption and small intestinal transit in critical illness. *Critical Care Medicine* 2011 Jun; 39(6):1282-1288. Relevant section in this thesis: Chapter 5.

Deane AM, Chapman MJ, Fraser RJ, Burgstad C, Besanko LK, Horowitz M. The effect of exogenous glucagon-like peptide-1 on the glycaemic response to small intestinal nutrient in the critically ill: a randomised double-blind placebo controlled cross-over study. *Critical Care* 2009 May 13; 13(3):R67. Relevant section in this thesis: Chapter 6.

Deane AM, Summers MJ, Zaknic AV, Chapman MJ, Fraser RJL, Di Bartolomeo AE, Wishart JM, Horowitz M Exogenous glucagon-like peptide-1 attenuates the glycaemic response to postpyloric nutrient infusion in critically ill patients with type-2 diabetes. *Critical Care* 2011 Jan 21; 15(1):R35. Relevant section in this thesis: Chapter 6.

Deane AM, Chapman MJ, Fraser RJL, Summers MJ, Zaknic AV, Storey JP, Jones KL, Rayner CK, Horowitz M. Effects of exogenous glucagon-like peptide-1 on gastric emptying and glucose absorption in the critically ill – relationship to glycaemia *Critical Care Medicine* 2010 May; 38(5):1261-9. Relevant section in this thesis: Chapter 6.

Deane AM, Wong GL Horowitz M, Zaknic AV, Summers MJ, Di Bartolomeo AE, Sim JA, Maddox AF, Bellon MS, Chapman MJ, Fraser RJL. Effects of erythromycin on small intestinal nutrient absorption and transit in critically ill patients *American Journal of Clinical Nutrition* (In Press). Relevant section in this thesis: Chapter 5.

A proportion of the work presented in this thesis has been submitted for publication in peer-reviewed journals. The section of the thesis where such work is included is provided below:

Di Bartolomeo AE, Chapman MJ, Zaknic AV, Summers MJ, Fraser RJ, Jones KL, Nguyen NQ, Rayner CK, Horowitz M, Deane AM. Comparative Effects of Intragastric and Postpyloric Nutrient Delivery in the Critically Ill *Manuscript under review*. Relevant section in this thesis: Chapter 5.

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ABBREVIATIONS USED IN THE THESIS

3-OMG	3-O-Methyl-Glucose
ADA	American Diabetes Association
ARDS	Acute respiratory distress syndrome
APD	antropylorduodenal
APACHE	Acute physiology and chronic health evaluation
AWs	Antral waves
CCK	Cholecystokinin
DPP-4	dipeptidyl peptidase-4
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
ex(9-39)NH_2	Exendin(9-39)amide
GEC	Gastric emptying coefficient
GH	Growth hormone
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GRV	Gastric residual volume
GTN	Glycel trinitrate
HbA_{1C}	Glycated haemoglobin
HPLC	High-performance liquid chromatograph
ICU	Intensive care unit
IPPWs	Isolated pyloric pressure waves
L-NAME	L-Nitro-arginine methyl ester
L-NMMA	L-Nitro-monomethyl-arginine
MMC	Migrating motor complex
MRI	Magnetic resonance imaging
NANC	Non-adrenergic non-cholinergic
NEFA	Non-esterified fatty acids
NH&MRC	National health and medical research council
NO	Nitric oxide
POC	Point-of-care
PN	Parenteral nutrition
PYY	Peptide YY
SGLT-1	Sodium glucose cotransporter-1