The Role of the Free Fatty Acid, Lauric Acid, in Appetite Regulation and its Potential as an Appetite-Suppressant

A thesis submitted by

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List of abbreviations

^{125}I	125 Iodine
Apo A-IV	Apolipoprotein A-IV
APD	Antropyloroduodenal pressure waves
AUC	Area under the curve
BMI	Body mass index
BSA	Bovine serum albumin
C4	Butyric acid, saturated fatty acid with 4 carbon atoms
C8	Caprylic acid, saturated fatty acid with 8 carbon atoms
C10	Decanoic acid, saturated fatty acid with 10 carbon atoms
C12	Lauric acid, saturated fatty acid with 12 carbon atoms
C18:1	Oleic acid, monounsaturated fatty acid with 18 carbon atoms
C18:2	Linoleic acid, polyunsaturated fatty acid with 18 carbon atoms
CCK	Cholecystokinin
CV	Coefficient of variation
GI	Gastrointestinal tract
GLP-1	Glucagon-like peptide-1
GLP-2	Glucagon-like peptide-2
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
ID	Intraduodenal
IPPWs	Isolated pyloric pressure waves
L-81	Pluronic L-81
LOX	Loxiglumide
MMC	Migrating motor complex
NaOH	Sodium hydroxide
NPY	neuropeptide Y
PP	Pancreatic polypeptide
PYY	Peptide YY
PWs	Pressure waves
PWSs	Pressure wave sequences
THL	Tetrahydrolipstatin
VAS	Visual analogue scale questionnaire

Thesis summary

The presence of nutrients, particularly fat, in the small intestine modulates gastrointestinal function and subsequent energy intake, and it is well established that the digestion of fat into free fatty acids is required for these effects to occur. Furthermore, the effects of fatty acids are dependent on their chain length. The research presented in this thesis relates to the effects of fatty acids, particularly lauric acid, on the regulation of gastrointestinal function and the suppression of energy intake.

One of the first studies in humans to evaluate the effect of fatty acid chain length established that fatty acids with ≥ 12 carbon atoms slow gastric emptying, while fatty acids with ≤ 10 carbon atoms have no effect, indicating that there may be a separation in the effects of fatty acids occurring between those with ≤ 10 and ≥ 12 carbon atoms. More recent studies in humans have determined that there are marked differences in the effects of intraduodenal lauric acid, a saturated fatty acid with 12 carbon atoms ("C12"), and decanoic acid, a saturated fatty acid with 10 carbon atoms ("C10), on the modulation of gastrointestinal motility, hormone secretion and energy intake. For example, C12, but not C10, markedly suppresses energy intake, modulates pressure waves in the antropyloroduodenal (APD) region and stimulates glucagon-like peptide-1 (GLP-1) secretion, while both C12 and C10 stimulate cholecystokinin (CCK) secretion, however, the effect of C12 was much greater. A previous study in humans has also shown that intraduodenal administration of a long-chain fatty acid, such as oleic acid, a monounsaturated fatty acid with 18 carbon atoms ("C18:1"), suppresses energy intake when compared with a short-chain fatty acid, such as capric acid, a saturated fatty acid with 8 carbon atoms ("C8"). While there have been no direct comparisons between fatty acids with 12 or more carbon atoms (eg C12 vs C18:1) on gastrointestinal function

and energy intake, there is evidence in animals that C12 may be more potent in suppressing energy intake than C18:1.

The first study presented in this thesis (Chapter 4) assessed the effects of intraduodenal C12 and C10 in healthy men on the gastrointestinal hormones; ghrelin, peptide YY (PYY), glucagon-like peptide-2 (GLP-2) and pancreatic polypeptide (PP). C12, but not C10, markedly stimulated the secretion of PYY and GLP-2 and suppressed ghrelin secretion, while both C12 and C10 slightly increased PP secretion.

The effects of intraduodenal C12 and C18:1 delivered at the same energy load (0.4 kcal/min) on APD motility, secretion of CCK and PYY and energy intake were compared in healthy males (Chapter 5). Both C12 and C18:1 stimulated isolated pyloric pressure waves (IPPWs), suppressed the number of antral pressure waves (PWs) and increased plasma CCK concentrations, with no differences between the two fatty acids. In contrast, while both C12 and C18:1 increased basal pyloric pressure and plasma PYY concentrations, C12 had a greater effect on basal pyloric pressure than C18:1, while C18:1 had a greater effect on PYY than C12. Interestingly, C12, but not C18:1, suppressed energy intake.

While a previous study in humans has shown that C12 markedly suppressed energy intake, this was associated with nausea in some subjects, hence, confounding the interpretation of the results. In order to determine whether the effects of C12 on energy intake were physiological, or related to nausea, a dose-response study was performed using loads ranging from: 0.1 – 0.4 kcal/min, but this was also associated with varying C12 concentrations (Chapter 6). C12 potently modulated APD motility, increased

plasma CCK and GLP-1 concentrations and suppressed energy intake in a dose-dependent manner, in the absence of nausea. However, as both load and concentration of the C12 solutions were varied, it was unclear whether these effects were load- or concentration-dependent. Therefore, the study in Chapter 7 assessed the response to (i) increasing loads of C12 (0.2 – 0.4 kcal/min), at a fixed concentration (56 mM) and (ii) increasing concentrations of C12 (40 – 72 mM), at a fixed load (0.4 kcal/min), on gastrointestinal function and energy intake. Increasing load, but not concentration, of C12 modulated gastrointestinal motility, increased plasma CCK and PYY concentrations and suppressed energy intake.

As both CCK and GLP-1 are secreted in response to nutrient ingestion, the study in Chapter 8 assessed whether CCK-8 and GLP-1 interacted in their effects on gastrointestinal function and energy intake. – Intravenous CCK-8 (1.8 pmol/kg/min) and GLP-1 (0.9 pmol/kg/min) were administered alone and in combination. At the doses evaluated, CCK-8 suppressed energy intake, decreased the number of antral and duodenal PWs and increased IPPWs, while GLP-1 only decreased antral and duodenal PWs, but had no effect on energy intake and IPPWs. The combination of CCK-8 and GLP-1 only decreased the number of duodenal PWs to a greater extent than either infusion alone, but this did not exceed the sum of the individual effects of CCK-8 and GLP-1.

A previous study has demonstrated that following intragastric administration of C12, the effects of C12 on gastrointestinal function, including suppression of antral contractions, relaxation of the proximal stomach and stimulation CCK secretion, which are associated with the suppression of energy intake, are still maintained. Hence, C12

may have the potential to be utilised as an oral appetite-suppressant. The study in Chapter 9 investigated the effects of increasing doses of orally ingested C12 between 2 – 6 g on appetite and energy intake. While oral ingestion of C12 had no effect on appetite perceptions, subsequent energy intake was markedly suppressed, in the absence of adverse effects, following the ingestion of 2 g and 6 g of C12.

In conclusion, intraduodenal infusion of C12 in humans has marked effects on gastrointestinal function and energy intake, specifically, the modulation of APD motility, secretion of CCK, GLP-1, GLP-2, PYY and PP, and suppression of ghrelin secretion and energy intake, when compared with fatty acids with both shorter and longer chain lengths. The effect of C12 on gastrointestinal function and energy intake is also dependent on load, but not concentration, of C12 administration. Moreover, oral ingestion of C12 also has a marked effect on the suppression of energy intake, in the absence of any adverse effects.

Statement of originality

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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Kate Feltrin

December 2007

Dedication

For my wonderful parents, Claude and Judy,

And

For my love, my best-friend, Troy

I am forever grateful

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