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**Effects of oral ingestion of sucralose on gut hormone response and appetite in healthy  
normal-weight subjects**

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Running head (38 characters): sweet taste receptors and gut hormones

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1 **Abstract** (234 words)

2 **Background:** The sweet taste receptor (T1r2+T1r3) is expressed by enteroendocrine L-cells  
3 throughout the gastrointestinal tract. Application of sucralose (a non-calorific, non-  
4 metabolisable sweetener) to L-cells *in vitro* stimulates glucagon-like peptide (GLP)-1  
5 secretion, an effect that is inhibited with co-administration of a T1r2+T1r3 inhibitor.

6 **Objective:** We conducted a randomised, single-blinded, cross-over study in eight healthy  
7 subjects to investigate whether oral ingestion of sucralose could stimulate L-cell derived  
8 GLP-1 and peptide YY (PYY) release *in vivo*.

9 **Methods:** Fasted subjects were studied on four study days in random order. Subjects  
10 consumed 50ml of either water, sucralose (0.083% w/v), a non-sweet, glucose-polymer  
11 matched for sweetness with sucralose addition (50% w/v maltodextrin + 0.083% sucralose)  
12 or a modified sham feeding protocol (MSF = oral stimulation) of sucralose (0.083% w/v).  
13 Appetite ratings and plasma GLP-1, PYY, insulin and glucose were measured at regular time  
14 points for 120 minutes. At 120 minutes, energy intake at a buffet meal was measured.

15 **Results:** Sucralose ingestion did not increase plasma GLP-1 or PYY. MSF of sucralose did  
16 not elicit a cephalic phase response for insulin or GLP-1. Maltodextrin ingestion significantly  
17 increased insulin and glucose compared to water ( $p < 0.001$ ). Appetite ratings and energy  
18 intake were similar for all groups.

19 **Conclusions:** At this dose, oral ingestion of sucralose does not increase plasma GLP-1 or  
20 PYY concentrations and hence, does not reduce appetite in healthy subjects. Oral stimulation  
21 with sucralose had no effect on GLP-1, insulin, or appetite.

22 **Keywords:** obesity, sucralose, sweetener, gut hormone, appetite

## 23 **Introduction**

24 Recently, there have been significant advances in our understanding of how hormonal signals  
25 released from the gastrointestinal (GI) tract interact with circuits within the central nervous  
26 system to control appetite and energy intake (Murphy and Bloom, 2006). The gut hormones  
27 peptide YY (PYY) and glucagon-like peptide (GLP)-1 are co-secreted from intestinal  
28 enteroendocrine L-cells and released post-prandially in proportion to the amount of energy  
29 ingested (Adrian et al., 1985; Ghatei et al., 1983; Le Roux et al., 2006). PYY and GLP-1 have  
30 both been shown to be satiety factors, reducing food intake when administered to rodents  
31 (Batterham et al., 2002; Challis et al., 2003; Chelikani et al., 2005a; Chelikani et al., 2005b;  
32 Chelikani et al., 2006; Halatchev et al., 2004; Talsania et al., 2005) and to humans  
33 (Batterham et al., 2002; Degen et al., 2005; Flint et al., 1998; Gutzwiller et al., 1999; Le  
34 Roux et al., 2006). The incretin effect of GLP-1, augmentation of insulin secretion in  
35 response to an oral glucose load, has been well characterised (Elrick et al., 1964). Secretion  
36 of PYY and GLP-1 is regulated by a complex neuro-humoral system in addition to direct  
37 nutrient contact with specific receptors expressed by intestinal L-cells. However, the  
38 mechanisms by which luminal nutrients stimulate the release of GLP-1 and PYY from L-cells  
39 remain poorly understood.

40 The two proteins T1r2 and T1r3 form a heterodimer and function together as a general sweet-  
41 taste receptor (Li et al., 2002; Nelson et al., 2001). T1r2+T1r3 is coupled to the G-protein  
42 gustducin, which mediates transduction of sweet taste signals (Wong et al., 1996). T1r, and  
43 the alpha subunit of gustducin ( $\alpha$ -gust), are co-localised with GLP-1 and PYY in  
44 enteroendocrine L-cells of the intestinal brush border membranes (Jang et al., 2007;  
45 Rozengurt et al., 2006; Sutherland et al., 2007). Recently, a key role for  $\alpha$ -gust and a  
46 functioning sweet-taste receptor in glucose stimulated GLP-1 secretion from the L-cell has

47 been demonstrated (Jang et al., 2007). Application of sucralose (a non-calorific, non-  
48 metabolisable sweetener) to human L-cells *in vitro* stimulated GLP-1 secretion and this effect  
49 was inhibited with co-administration of a T1r3 inhibitor. This evidence supports a new  
50 signaling mechanism which regulates gut hormone secretion via the sweet-taste receptor  
51 T1r2+T1r3 in the GI tract.

52 One proposed factor in the increasing prevalence of obesity and type 2 diabetes is an  
53 increased consumption of processed foods containing high levels of sucrose and fructose  
54 (Bray et al., 2004; Elliott et al., 2002; Raben et al., 2002). To offset this, the food industry has  
55 attempted to replace sugars with artificial sweeteners. The ability of non-calorific sweeteners  
56 to enhance endogenous gut hormone release would represent a potentially exciting  
57 opportunity for their addition to foods as agents to control glucose homeostasis and appetite  
58 regulation in populations at risk of type 2 diabetes and obesity.

59 The aim of this study is to investigate whether oral ingestion of sucralose, at a dose that  
60 would be consumed in a normal diet, increases circulating GLP-1 or PYY concentrations in  
61 man.

62

## 63 **Subjects and Methods**

### 64 Subjects

65 Eight normal-weight, healthy volunteers were locally recruited. All were non-smokers, aged  
66 22-27y (seven females and one male) with a stable body weight and a body mass index  
67 ranging from 18.8 to 23.9 kg/m<sup>2</sup>. Persons who disliked the study food, who had food allergies  
68 or food restrictions, who were taking medication that was likely to affect taste, smell or  
69 appetite or who reported recent weight loss or weight cycling were excluded. Subjects were

70 screened using the standard Dutch Eating Behaviour questionnaire (Van Strien et al., 1986)  
71 and SCOFF questionnaire (Morgan et al., 2000) and were excluded if they demonstrated  
72 abnormal eating behaviour. Female volunteers attended all study days within the follicular  
73 stage of the menstrual cycle.

74 The study was conducted with local ethical approval (project registration number:  
75 07/Q0406/62). Written informed consent was obtained from all volunteers and the study was  
76 performed in accordance with the Declaration of Helsinki.

77

#### 78 Study design

79 The study had a randomised, single-blinded, cross-over design. Subjects were randomly  
80 assigned to receive one of four solutions on four separate study sessions. Study sessions  
81 lasted from 0830h until 1230h with at least three days between sessions. Subjects were asked  
82 to refrain from drinking alcohol and to keep evening meals and activity levels as similar as  
83 possible the day before each test session and to fast from 2100h, consuming only water.

84 On arrival at the study centre subjects were asked to be seated and to relax for 30 minutes  
85 following placement of the intravenous cannula. After two baseline blood samples subjects  
86 completed one of four experimental manipulations. Subjects ingested, in a single swallow,  
87 50mL of either water (W), sucralose (S; 0.083% w/v, 2mmol/L Splenda®, Tate and Lyle  
88 PLC, Southampton, UK) or the positive control maltodextrin (MD) which was matched for  
89 sweetness with sucralose (50% w/v Polycose®, Abbott Laboratories Ltd, US, plus 0.083%  
90 sucralose). Each was followed by a one minute period of modified-sham-feeding (MSF)  
91 protocol of the same solution that was swallowed. The fourth experimental manipulation was  
92 designed to ascertain the involvement of stimulation of the sweet-taste receptors within the

93 oral cavity independently of the sweet-taste receptors throughout the GI tract. In this instance  
94 subjects consumed 50mL water followed by the one-minute MSF of the sucralose solution  
95 (WS; 0.083% w/v sucralose). The test solutions used are described in Table 1. The MSF  
96 protocol involved drawing the solution up into the mouth through a straw, moving it around  
97 in the mouth and then spitting it out, doing so repeatedly until the entire volume of 200mL  
98 was finished and the one minute time limit was up. In order to investigate the cephalic effects  
99 of sucralose, the MSF was performed after ingestion of the test solution to ensure that no  
100 residual sucralose would be swallowed with the subsequent ingestion of water in the WS  
101 manipulation.

102 The dose of sucralose was chosen to represent a normal dietary load and the total volume  
103 ingested was kept to a minimum, as it is known that ingestion of large volumes of water  
104 alone can induce a gut hormone response (Christofides et al., 1979). Maltodextrin (a five  
105 polymer chain of glucose) was used to assess the effect of glucose on gut hormone release  
106 without the potential confounder of high concentrations of glucose effecting gastric emptying.  
107 The expectorate from the MSF was weighed to ensure compliance with the protocol. Blood  
108 samples and visual analogue scores (VAS) pertaining to subjective feelings of appetite, were  
109 taken for a further two hours. After the last blood sample at 120 minutes, a test meal of  
110 known energy content was given in excess and subjects were asked to eat until comfortably  
111 full. Energy intake was calculated from the weight of food eaten.

112

### 113 Blood samples

114 Two baseline blood samples were taken at -15 and 0 minutes before consumption of test  
115 solutions, then further samples were taken at 15, 30, 45, 60, 90 and 120 minutes after

116 consumption of test solutions. For analysis of the cephalic phase insulin release (CPIR) and  
117 the cephalic phase GLP-1 response, blood samples were also taken at 2, 4, 6, 8 and 10  
118 minutes for insulin and GLP-1 analysis only. Blood was collected in lithium heparin tubes  
119 containing 5000 kallikrein units of aprotinin (200 $\mu$ L; Trasylol; Bayer) and immediately  
120 centrifuged at 4°C. Plasma was separated and stored at -20°C until analysis.

121

### 122 Appetite ratings

123 Subjective feelings of appetite were assessed at -15, 0, 15, 30, 45, 60, 90 and 120 minutes  
124 using VAS (Flint et al., 2000) with questions pertaining to desire to eat, hunger and  
125 prospective food consumption. Subjects were also asked to score the palatability and  
126 sweetness of the test solutions. Subjects marked their answers to the questions on scales of  
127 100mm in length anchored at either end with the most positive and the most negative  
128 response. The distance along the scale that the subjects placed their mark was measured from  
129 one end and the reading in millimeters was recorded.

130

### 131 Biochemical analyses

132 All samples were assayed in duplicate and in a single assay to eliminate inter assay variation.  
133 Plasma PYY and GLP-1 were assessed using an established in-house radioimmunoassay  
134 (RIA) described previously (Adrian et al., 1985; Kreymann et al., 1987). The detection limit  
135 of the PYY and GLP-1 assays was 2.5pmol/L and 7.5pmol/L with an intra-assay coefficient  
136 variation (CV) of 5.8% and 5.4% respectively. Insulin was measured using AxSYM analyser  
137 (Abbott Diagnostics, Maidenhead, UK). Sensitivity was 7 pmol/L with an intra-assay CV of



138 2.6%. Plasma glucose was measured using an Abbott Architect ci8200 analyser (Abbott  
139 Diagnostics, Maidenhead, UK). Sensitivity was 0.3mmol/L and intra-assay CV was 1%.

140

#### 141 Statistics

142 All data are represented as mean values  $\pm$  SEM. Plasma hormone and glucose concentrations  
143 were adjusted from baseline and represented as time course from change from baseline.

144 Incremental area under the curve (iAUC) was calculated over baseline by the trapezoidal rule.

145 Data for energy intake and iAUC were tested for normality and analysed using repeated

146 measures one-way ANOVA with Bonferroni's test for *post hoc* comparisons (GraphPad

147 Prism 4.03 Software, San Diego, USA). In all cases  $P < 0.05$  was considered to be statistically

148 significant.

149

#### 150 **Results**

##### 151 Validation of MSF

152 After all test solutions, the expectorate weight was greater than the weight of the MSF  
153 solutions sipped due to the addition of saliva indicating a successful MSF with minimum  
154 swallowing of test solutions.

155 The water solution was significantly less sweet than the remaining three test solutions ( $70.9 \pm$   
156  $3$  mm [WS],  $P < 0.001$ ;  $65.9 \pm 10.8$  mm [S],  $P < 0.01$ ;  $73.1 \pm 8$  mm [MD],  $P < 0.001$  vs.  $5.9 \pm 2$   
157 mm [W];  $n=8$ ). The WS, S and MD solutions were rated as having the same sweetness and  
158 palatability ( $42.8 \pm 8.9$  mm [WS];  $36.8 \pm 10$  mm [S];  $38.1 \pm 8.5$  mm [MD],  $26.1 \pm 6$  mm [W];  
159  $n=8$ ).

160

161 *Appetite and food intake*

162 For the two hour period following administration of the test solutions, there was no  
163 significant difference in the  $iAUC_{(0-120min)}$  of subjective feelings of appetite (Table 2). Two  
164 hours after consumption of test solutions, there was no significant difference in energy intake  
165 or water intake at the buffet meal (Table 2).

166

167 *Hormones and glucose*

168 Plasma insulin and GLP-1 did not show any significant change during the first 10 min after  
169 the MSF of any solution (Table 2).  $iAUC_{(0-120min)}$  for plasma GLP-1 and PYY concentrations  
170 were similar in all four groups. The MD group had a significantly higher  $iAUC_{(0-120min)}$  of  
171 insulin and glucose concentrations compared with water, but there was no difference between  
172 any other solution tested (Figure 1 and Table 2).

173

174 **Discussion**

175 In the present study, we show that oral ingestion of a common dietary dose of the non-  
176 calorific, artificial sweetener sucralose does not increase plasma GLP-1 or PYY  
177 concentrations nor does it affect subjective feelings of appetite or energy intake at the next  
178 meal in healthy volunteers. This study mimics the physiological intake of a sweetened  
179 solution. Our data are in accord with recently published human data (Ma et al., 2009) and *in*  
180 *vivo* rat data (Fujita et al., 2009) in which sucralose ingestion failed to stimulate a rise in two  
181 circulating incretin hormones, GLP-1 and the K cell derived glucose-dependent

182 insulinotropic polypeptide (GIP). Ma *et al.* administered sucralose nasogastrically to healthy,  
183 normal weight volunteers and observed no effect on plasma GLP-1 or GIP concentrations  
184 (Ma *et al.*, 2009). Similarly, Fujita *et al.* demonstrated in rats that in contrast to sucrose  
185 gavage, oral gavage of sucralose did not induce a rise in plasma GLP-1 (Fujita *et al.*, 2009).  
186 The only other published study to investigate the acute effect of oral sweetener ingestion on  
187 gut hormone release in humans used the sweetener aspartame. Although, ingestion of  
188 encapsulated aspartame was associated with a reduction in subsequent food intake, this effect  
189 did not seem to be mediated by GLP-1 release (Hall *et al.*, 2003). We chose not to  
190 encapsulate sucralose in our study, as it remains intact throughout the GI tract and very little  
191 is absorbed (Grice and Goldsmith, 2000). Therefore, sucralose may stimulate receptors on  
192 more distal L cells throughout the GI tract.

193 We did not observe a plasma GLP-1 response following ingestion of maltodextrin plus  
194 sucralose. GLP-1 response to glucose seems to be dependent on glucose been present in the  
195 distal duodenum where L-cells are present (Parker *et al.*, 2010). In this experiment we used  
196 relatively low amount of a glucose polymer which is cleared efficiently in the proximal  
197 duodenum before it can elicit a gut hormone response.

198 Oral ingestion of two non-calorific sweeteners, sucralose plus acesulfame K, followed by an  
199 oral glucose tolerance test, produces higher plasma peak GLP-1 concentrations compared to  
200 ingestion of water followed by an oral glucose tolerance test in healthy normal weight  
201 subjects (Brown *et al.*, 2009). Consistent with this sucralose plus glucose has an additive  
202 stimulatory effect on GLP-1 secretion from murine primary L-cells compared to sucralose or  
203 glucose alone (Reimann *et al.*, 2008). Taken together these studies suggest that non-calorific  
204 sweeteners and sugars may act synergistically to stimulate GLP-1 release from L-cells. In the  
205 current study, the maltodextrin solution was matched for sweetness by addition of sucralose.

206 Therefore we cannot exclude a synergistic effect of maltodextrin and sucralose on plasma gut  
207 hormone concentrations, if a gut hormone response had occurred. It would be interesting to  
208 compare the effects of maltodextrin alone, without any match for sweetness, to the  
209 combination of maltodextrin plus sucralose to assess any additive effect of sucralose and  
210 maltodextrin on GLP-1 release.

211 Furthermore, we show that sucralose ingestion does not affect plasma glucose and insulin.  
212 This is consistent with previous human studies in which no effect on plasma glucose and  
213 insulin was observed following ingestion of encapsulated sucralose in diabetic patients (Grotz  
214 et al., 2003) or following intragastric infusion of sucralose in healthy subjects (Ma et al.,  
215 2009). Similarly, oral gavage of sucralose in rats did not improve glucose homeostasis  
216 following an intraperitoneal glucose tolerance test (Fujita et al., 2009), suggesting that there  
217 was no incretin effect mediated by the sucralose gavage.

218 Our study is the first to investigate the cephalic phase GLP-1 and insulin responses to  
219 sucralose. We demonstrate that stimulation of the oral cavity with a sucralose-sweetened  
220 solution does not lead to an early (0-10 min) increase in plasma GLP-1 and does not affect  
221 subsequent food intake. This is in keeping with previous studies which have not demonstrated  
222 a cephalic phase GLP-1 response to either ingestion of a mixed meal (Ahren and Holst, 2001)  
223 or to a sham fed meal (Luscombe-Marsh et al., 2009). Furthermore, we show that sucralose  
224 does not elicit a preabsorptive insulin response. This is consistent with previous studies using  
225 a similar MSF protocol to assess the ability of non-calorific sweeteners such as aspartame and  
226 saccharin to induce a CPIR in humans (Abdallah et al., 1997; Teff et al., 1995).

227 The concentration of sucralose used in the present study (2mmol/L) was chosen to be both  
228 palatable and within the dose range (1-5mmol/L) previously shown to trigger GLP-1 release  
229 from intestinal L-cells *in vitro* (Jang et al., 2007). However, with ensuing dilution in the gut

230 lumen post-ingestion, it is possible that the concentration of sucralose reaching the small  
231 intestine was below 2mmol/l, which may have been insufficient to stimulate GLP-1 secretion.

232 An alternative explanation for our findings is that sucralose does not stimulate GLP-1 release  
233 from intestinal enteroendocrine cells. In support of this, recent *in vitro* studies failed to  
234 demonstrate an effect of sucralose on GLP-1 (Reimann et al., 2008) from enteroendocrine  
235 cells using a similar sucralose concentration to that used in the current study. Furthermore, a  
236 recent *in vivo* study has shown that intragastric infusion of up to 40mmol/L sucralose does  
237 not induce GLP-1 secretion in humans (Ma et al., 2009). Together with our data, these studies  
238 suggest that there is no measurable acute enhancement of GLP-1 or PYY release *in vivo*  
239 following oral ingestion of sucralose. The reason for the apparent disparity of the effect of  
240 sucralose on gut hormone release *in vitro* and *in vivo* is not clear and requires further  
241 investigation.

242 In summary, we have shown that oral ingestion of sucralose does not elicit a cephalic phase  
243 GLP-1 or insulin response nor increase post-ingestive plasma GLP-1 or PYY concentrations,  
244 and therefore does not subsequently affect appetite. Our findings, using a dietary dose of  
245 sucralose, do not support the proposal that stimulation of the sweet taste receptor in the GI  
246 tract can stimulate release of GLP-1 and PYY from enteroendocrine L-cells.

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### **Contributions of the authors:**

H.E.F. and V.P. designed the experiment, collected and analysed data and wrote the manuscript. N.M.M. helped with the writing of the manuscript. M.S. contributed to the data analysis. M.A.G, G.S.F and S.R.B. provided significant advice.

### **Conflict of interest:**

The authors do not declare any conflict of interest.

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**Table 1.** Description of the test solutions used on the four study days.

<b>Study day</b>	<b>Test solution ingested</b> (Volume=50ml)	<b>Test solution used for the one-minute MSF</b> (Volume=200ml)
water (W)	water	water
cephalic sucralose (WS)	water	sucralose dissolved in water
sucralose (S)	sucralose dissolved in water	sucralose dissolved in water
maltodextrin+sucralose (MD)	maltodextrin plus sucralose dissolved in water	maltodextrin plus sucralose dissolved in water

**Table 2.** Incremental AUC data for plasma hormones, glucose and appetite scores measured between 0 and 120 minutes (unless specified) and energy and water intake at the buffet meal.

	<b>W</b>	<b>WS</b>	<b>S</b>	<b>MD</b>
<b>Insulin</b> <sub>(0-10min)</sub> (pmol.min/L)	171 ± 60	235 ± 83	70 ± 25	68 ± 24
<b>GLP-1</b> <sub>(0-10min)</sub> (pmol.min/L)	882 ± 113	948 ± 171	922 ± 132	658 ± 78
<b>Glucose</b> (mmol.min/L)	33.5 ± 6.9 <sup><b>a</b></sup>	51 ± 12.5 <sup><b>b</b></sup>	25.3 ± 20.4 <sup><b>c</b></sup>	122.3 ± 17.5
<b>Insulin</b> (pmol.min/L)	287 ± 331 <sup><b>c</b></sup>	-471 ± 132 <sup><b>c</b></sup>	-459 ± 352 <sup><b>c</b></sup>	5669 ± 519
<b>GLP-1</b> (pmol.min/L)	-675 ± 1610	-248 ± 784	-359 ± 401	415 ± 610
<b>PYY</b> (pmol.min/L)	-179 ± 119	-128 ± 119	-56 ± 192	283 ± 185
<b>Hunger</b> (mm.min)	1724 ± 322	1641 ± 336	1993 ± 199	2017 ± 472
<b>Desire to eat</b> (mm.min)	1376 ± 216	1128 ± 275	1330 ± 458	1441 ± 461
<b>Prospective food consumption</b> (mm.min)	1318 ± 305	1623 ± 266	2002 ± 247	1676 ± 441
<b>Energy intake</b> (kJ)	2355±227	2417±222	2597±277	2460±167
<b>Water intake</b> (mL)	267.0±69.0	250.7±45.1	291.8±49.8	305.0±49.6

W=water, WS= cephalic sucralose, S=sucralose, MD=maltodextrin+sucralose. Data are represented as mean ± SEM. **a** = p<0.05 compared to MD, **b** = p<0.01 compared to MD, **c** = p<0.001 compared to MD. n=8.

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**Figure legends**

**Figure 1.** Change in plasma A) GLP-1, B) PYY, C) insulin and D) glucose from baseline following administration of test solutions (n=8). ●=water, ○=cephalic sucralose, ■=sucralose, □=maltodextrin+sucralose. Data are represented as mean ± SEM.

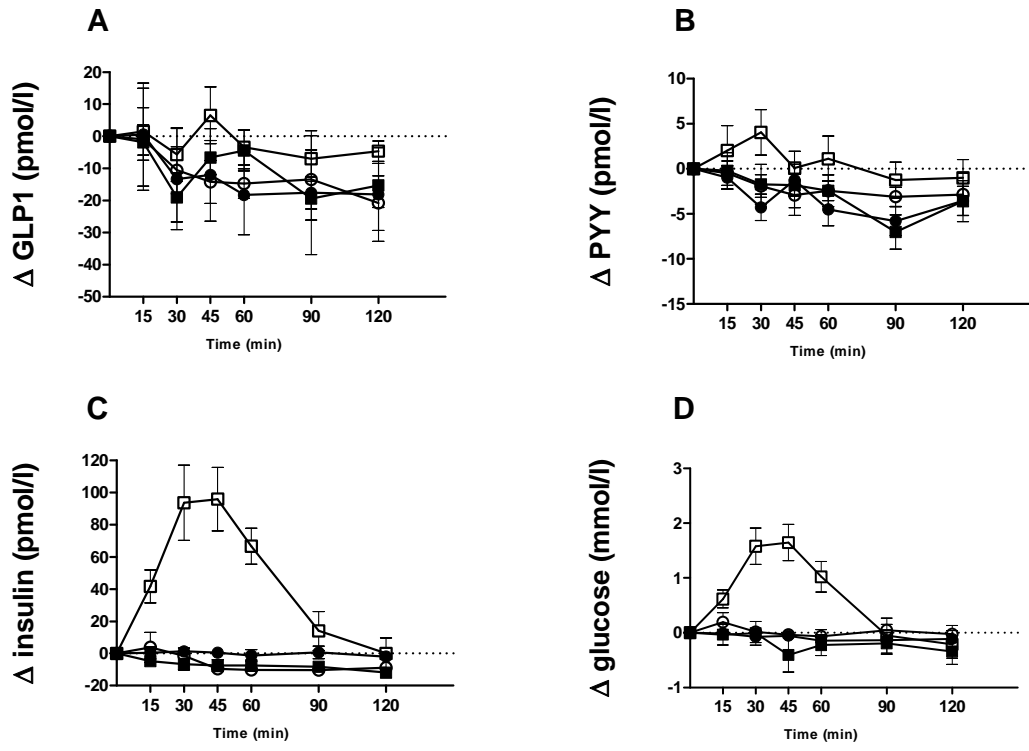


Figure 1