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Paradoxical second-meal phenomenon in the acute post-exercise period

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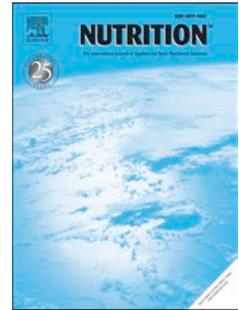
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2

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4

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27

28 **Abstract**

29 Attenuating blood glucose excursions in the postprandial state has the capacity to reduce the

30 risk of cardiovascular disease, type 2 diabetes and mortality, even in apparently healthy

31 populations. Almost a century ago it was reported that oral glucose tolerance is improved by

32 prior glucose consumption. This was termed the second-meal phenomenon and is also seen

33 with consumption of mixed-macronutrient containing meals. In this context a number of

34 mechanisms probably contribute to the attenuation of glycemia, including: gastric emptying,

35 early-phase insulin secretion, hepatic glucose output and muscle glucose uptake. More

36 recently, a paradoxical second-meal phenomenon has been observed in the immediate post-

37 exercise period whereby prior meal consumption deteriorated glucose tolerance. The

38 mechanisms regulating the post-exercise second-meal phenomenon are less clear, but are

39 likely to involve an increase in intestinal absorption, greater hepatic glucose output, and

40 under circumstances of muscle-damage, reductions in muscle glucose uptake. Further work is

41 required to confirm these mediating factors and to characterize the time-course of this

42 paradox, which is likely to only exist within the first 4 h following exercise. Critically, this

43 acute post-exercise phenomenon should be maintained in the perspective of the benefits of

44 chronic exercise training, which for the majority of individuals improves glycemic control

45 and reduces many health risks including those associated with exaggerated postprandial

46 glycemia.

47

49

50

51
Introduction

53 Investigating glycemic responses to food ingestion is pertinent to all individuals due to the

54 strong links that glucose tolerance has with cardiovascular disease (CVD), type 2 diabetes

55 and mortality [1]. Even in populations considered healthy (fasting and 2 h postprandial

56 glucose < 6.1 and < 7.8 mmol/L, respectively), those with higher postprandial glucose

57 concentrations relative to fasting, have a ~10-20% increased risk of heart disease or stroke

58 [2]. Accordingly, studying glucose tolerance is appropriate to all individuals across the

59 metabolic health spectrum, from those with diagnosed type 2 diabetes, to those with

60 impaired, and normal, glucose tolerance. That postprandial glycemia is more strongly

61 associated with mortality than fasting glycemia reflects the relative importance of this

62 measure. This review discusses mechanisms underlying a well-established postprandial

63 glycemic effect seen in response to sequential meals known as the second-meal phenomenon,

64 and proceeds to describe a more recent paradoxical second-meal phenomenon, revealed in the

65 immediate post-exercise period.

66

Regulation of blood glucose homeostasis

68 Before interventions are discussed, the regulation blood glucose concentration will be briefly

69 reviewed. Circulating glucose concentrations represent the dynamic balance between

70 endogenous glucose appearance (from hepatic glycogenolysis and gluconeogenesis),

71 exogenous glucose appearance (via the intestine), and glucose disappearance (into tissues).

72 After an overnight fast, the amount of glucose in circulation is fairly constant at ~4.6 g in an

73 80 kg individual [3]. Hypothetically, if no regulatory mechanisms existed, it has been

74 calculated that the carbohydrate content of a typical meal would raise blood glucose

Page 3

75 concentration more than 8-fold [4]. However, at least in healthy people, synchronized

76 regulation means that blood glucose concentration rises to ~60% above its fasting value [4].

77 The regulation of blood glucose concentration in response to carbohydrate ingestion

78 transpires at a number of levels including: gastric emptying, intestinal absorption, splanchnic

79 and peripheral perfusion, and rates of tissue glucose uptake, which are all under some

80 hormonal control.

81

82 A hormone of great importance in glycemia is insulin, which reduces blood glucose

83 concentrations by suppressing hepatic glucose output [5] and stimulating muscle (and to

84 lesser degrees hepatic and adipose) glucose uptake. Insulin-induces translocation of the

85 glucose transporter isoform 4 (GLUT4) to the cell membrane surface (in the absence of

86 insulin, ~90% remain in intracellular vesicles [6]), allowing more glucose to enter the cell

87 [7]. Muscle is the tissue of greatest significance with regards to postprandial glucose uptake,

88 responsible for up to 90% of glucose disposal [8].

89

90 Gastrointestinally-derived hormones also make important contributions. Namely, glucose-

91 dependent insulinotropic peptide (formerly known as gastric inhibitory polypeptide; GIP) and

92 glucagon-like peptide-1 (GLP-1). Enteroendocrine cells in the intestine secrete these peptides

93 in response to nutrient exposure [9-11] and both these peptides potently stimulate insulin

94 secretion [12]. Thus, oral ingestion of food produces divergent insulin secretory and

95 sensitivity responses compared to intravenous glucose infusions, as direct contact of nutrients

96 with intestinal cells influences insulin secretion and action [13, 14]. Thereby having obvious

97 implications for interpreting studies using intravenous methods of glucose delivery and oral

98 glucose tolerance tests (OGTT) using glucose only.

99

100 **The second-meal phenomenon**

101 Western eating patterns typically result in the consumption of at least 3 meals per day [15].

102 With this in mind, studying responses to sequential food intake (as opposed to single meals)

103 is vital to translate laboratory findings into daily life [16]. Sequential OGTTs led to the

104 discovery of the second-meal phenomenon, which describes the improved glucose tolerance

105 seen after consumption of a prior glucose load. This was first observed in 1919 [17] and was

106 subsequently replicated [18] and termed the "Staub-Traugott" effect.

107

108 This effect is evident in those with and without type 2 diabetes [19-21] and in response to

109 intravenous glucose infusion [22]. Most relevant for practical application, is that this

110 response is seen with mixed-macronutrient meals [21, 23]. The efficacy of the response to

111 sequential-meals is dependent on the composition of the prior meal. For instance, a

112 moderately fatty breakfast tends to increase the glucose area under the curve (AUC) in

113 response to a standard lunch ($P = 0.08$), and is significantly higher than after a low-fat

114 breakfast ($P = 0.03$) [24]. This effect is also detectable in OGTT performed in the morning,

115 with macronutrient manipulation of an evening meal [25]. A higher glycemic index (GI)

116 and/or lower fermentable carbohydrate content of a prior meal can also increase the glycemic

117 response to a second, standard meal [26]. The mechanisms that underlie the second-meal

118 phenomenon at rest likely involve a combination of delayed gastric emptying, enhanced

119 insulin secretion, suppression of hepatic glucose production and enhanced muscle glucose

120 uptake (Figure 1).

121

122   Prior consumption of fat or protein slows gastric emptying of a subsequent carbohydrate-rich

123   meal, doubling the time to clear 50% of stomach content (known as T50 [19, 27]). Both these

124   studies also found greater postprandial responses of plasma GLP-1 [19, 27], which slows

125   gastric emptying [28] and potentiates insulin secretion [12].

126

127   Potentiated early-phase insulinemia following sequential meals is apparent [29] and is likely

128   due to priming of pancreatic β-cells by prior insulin exposure, along with suppressed

129   pancreatic NEFA exposure and increased GLP-1 concentrations. Evidence for these

130   mechanisms is provided by the potentiation of insulin secretion (by 32%) in response to

131   intravenous glucose with prior insulin infusion. Furthermore, insulin potentiation is

132   somewhat preserved (but attenuated to a 20% increase) when intralipid-heparin is co-infused

133   to maintain high NEFA concentrations [30]. This eliminates confounding from prolonged (>6

134   h) fatty acid exposure to β-cells, which inhibits pancreatic insulin secretion [31].

135

136   Bonnucelli *et al.* employed triple tracer techniques to reveal glucose kinetics during

137   sequential glucose ingestion (separated by 180 min) [32]. A suppression of endogenous

138   glucose production along with insulin potentiation, almost entirely accounted for the second-

139   meal effect observed in this study. Neither exogenous glucose appearance rates, nor glucose

140   disappearance rates were influenced. This contrasts with other work showing that oral

141   glucose loads (of either 15 or 25 g) delivered ~100 min prior to a euglycaemic,

142   hyperinsulinaemic clamp improve whole-body insulin sensitivity, as evidenced by a ~40%

143   greater glucose infusion rate [33]. This is also supported by the evidence of greater muscle

144   glycogen storage with the second-meal effect, in the presence of comparable insulinemia

145   [21]. The discrepancies between Bonnucelli *et al.* [32] and those showing delayed gastric

146 emptying (thus influencing exogenous appearance [19, 27]) and enhanced glucose

147 disappearance rate [21, 22, 33] can be explained by additional nutrients, and the time-delay

148 between sequential ingestive events.

149

150 Glucose tolerance is improved with the ingestion of sequential meals. This is likely due to a

151 combination of factors including slower gastric emptying (slowing exogenous glucose

152 appearance), combined with increased early-phase insulin secretion, reduced endogenous

153 glucose output from the liver, and enhanced glucose clearance by muscle (Figure 1).

154

155 **Post-exercise glucose tolerance**

156 Exercise produces large changes in substrate fluxes, dependent on intensity and duration of

157 exercise. Carbohydrates provide a major contribution to energy expenditure during moderate-

158 intense endurance exercise in the forms of muscle glycogen and plasma glucose [34].

159 Accordingly, 30 min of treadmill running at 70% $\dot{V}O_2max$ (maximal oxygen consumption)

160 depletes muscle glycogen by ~30% [35]. Insights gained from ^{13}C nuclear magnetic

161 resonance spectroscopy reveal that 90 min of cycling [at 70% $\dot{V}O_2peak$ (peak oxygen

162 consumption)] reduces muscle and hepatic glycogen reserves by ~60% and ~40%,

163 respectively [36]. The drive to replenish glycogen depots post-exercise leads changes in

164 muscle and liver metabolism that have consequences for postprandial glucose kinetics.

165

166 It is well-established that exercise increases muscle glucose uptake independent of insulin

167 (for a recent comprehensive review see Richter and Hargreaves [37]). Muscle insulin

168 sensitivity is also improved, which persist following full glycogen replenishment [38],

169 suggesting the drive to replenish glycogen is not the only explanation for post-exercise

170 insulin sensitivity enhancement. Elevated post-exercise muscle glucose uptake makes it

171 attractive to speculate that oral glucose tolerance would also be improved; however this is not

172 always the case. Acute endurance-type exercise tends to deteriorate [39-42], or not

173 significantly affect [43, 44] oral glucose tolerance in healthy people. Differences between

174 studies, such as the nutritional status of participants prior to the exercise bout (fasted/fed),

175 and the time delay between exercise and glucose tolerance assessment, may contribute to the

176 equivocality. A recent study addressed the issue of nutritional status by evaluating the

177 response to consumption of a mixed-macronutrient beverage (16 g protein, 56 g carbohydrate

178 and 8 g fat) following exercise in the fasted and fed state [45]. Healthy males completed 4

179 trials in a randomized, crossover design. Trials consisted of a fasted rest trial (FR) a breakfast

180 rest trial (BR), a fasted exercise trial (FE) and a breakfast exercise trial (BE). The porridge-

181 based breakfast (19 g protein, 67 g carbohydrate and 11 g fat) was provided 2 h prior to

182 exercise, which comprised treadmill running at 60% $\dot{V}O_2$peak for ~60 min (until 2.9 MJ had

183 been expended). In the fasted state, glucose tolerance was similar between exercise and rest

184 trials supporting some previous findings. Following breakfast consumption however, exercise

185 produced a surprising 15% *increase* in the blood glucose AUC, relative to rest (Figure 2; $P =$

186 0.012). Peak blood glucose concentrations were also greater (~16%; P = 0.03) in the BE trial

187 compared to BR. This post-exercise effect is somewhat enigmatic on first impression and

188 provokes an interesting discussion into the ostensible mechanisms that underlie this

189 paradoxical phenomenon. One interesting point is that impaired glucose tolerance was

190 present even though there was apparent potentiation of early phase insulin secretion, as

191 indicated by the significantly higher serum insulin concentrations 15 min post-drink

192 consumption in BR and BE trials (Figure 3).

193

194 **Mechanisms to explain the paradoxical post-exercise second-meal phenomenon**

195 Cycling exercise (using predominantly lower-limb musculature) does not influence basal

196 glucose uptake in the forearm (comprising non-exercised muscle), and insulin-stimulated

197 glucose uptake is in fact *impaired* [46]. This may be due to intramuscular lipid accumulation

198 [47] from high NEFA exposure and low lipid utilization during exercise. Therefore the

199 impact of exercise on whole-body glucose disposal is dependent on recruitment of large

200 muscle groups, with non-exercised muscle in fact dampening the enhancement of whole-

201 body insulin sensitivity produced by exercised muscle. Notwithstanding this, whole-body

202 glucose uptake is enhanced after endurance exercise in the fasted state [42]. Whether

203 consumption of a meal, prior to exercise, influences lipid accumulation and subsequent

204 insulin resistance in non-exercised muscle remains to be determined. Moreover, tracer studies

205 in both canines [48] and humans [42], indicate a larger role of increased glucose appearance

206 in influencing oral glucose tolerance.

207

208 Rose *et al.* demonstrated that postprandial whole-body glucose disappearance is enhanced by

209 24% when exercise precedes an OGTT [42]. This was however, completely superseded by a

210 30% elevation in the glucose appearance, which was primarily due to exogenous (orally-

211 derived) glucose appearance, although endogenous glucose appearance (hepatically-derived),

212 was also higher following exercise. Changes in gastric emptying rates are not evident post-

213 exercise at the intensities used in the studies described [49, 50], leaving perfusion and/or

214 intestinal permeability to explain the greater rates of exogenous glucose appearance.

215 Intestinal perfusion positively associates with intestinal glucose absorption [51] and exercise

216 increases subsequent postprandial splanchnic perfusion by 15-35% [52]. Moreover, food

217 consumption prior to exercise increases splanchnic perfusion during exercise [49], providing

218 a possible avenue through which prior nutritional status influences glucose tolerance in the

219 post-exercise period. Although, using arterial-venous difference and tracer techniques in

220 dogs, it was shown that intestinal glucose absorption is enhanced following exercise, in spite

221 of the absence of a significant change in splanchnic perfusion [48]. Therefore it remains

222 inconclusive as to whether changes in blood flow contribute to the post-exercise second-meal

223 phenomenon in humans, leaving an elevated intestinal absorption rate as a probable mediator.

224

225 Increased exogenous glucose appearance could also be due to intestinal barrier dysfunction.

226 Cycling (70% maximum power output) for 60 min increases small intestine permeability

227 [53], with evidence of intestinal cell damage (indicated by elevated circulating concentrations

228 of intestinal fatty acid binding protein) which positively correlate with the degree of

229 splanchnic hypoperfusion. These findings suggest that in fact a reduction in splanchnic

230 perfusion is responsible for intestinal damage and permeability to carbohydrates, which

231 contradicts the previous discussion regarding splanchnic perfusion. However, reduced

232 splanchnic blood flow is only pertinent to high-intensity exercise, as no hypoperfusion is

233 evident at 55% $\dot{V}O_2$peak [49].

234

235 There are other candidates for inducing intestinal glucose absorption and/or permeability

236 following lower intensity exercise. These include heat [54] and hormonal changes involving

237 epinephrine [55, 56] and vasoactive intestinal peptide [40]. Regarding diet, intake of fiber,

238 fat, protein and drinks of high-osmolality are associated with self-reported gastrointestinal

239 distress during triathlon [57]. Thus, gastrointestinal damage may occur from mechanical

240 stress, particularly during running, potentially exasperated by the presence of food in the

241 gastrointestinal tract.

242

243 Regardless of mechanisms and consequences for glucose tolerance, the accelerated

244 exogenous glucose appearance following exercise could be viewed as advantageous in

245 assisting (along with muscle GLUT4 translocation and glycogen synthase activity) rapid

246 muscle glycogen replenishment post-exercise. Indeed, moderate-intensity (~60% $\dot{V}O_2max$)

247 exercise prior to consumption of high-carbohydrate meals increases postprandial glycemia

248 and enhances glycogen storage and balance [39].

249

250 Muscle glycogen is thought to regulate glucose uptake in part, by inhibiting GLUT4

251 translocation and/or hexokinase activity from glycogenolysis-induced elevations in

252 intramuscular glucose-6-phosphate concentrations [37]. With this in mind, it would seem

253 intuitive that elevated pre-exercise muscle glycogen concentrations (from prior meal

254 consumption) may persist following exercise and contribute to lower glucose uptake relative

255 to fasted exercise. This is however, unlikely to be the case in the phenomenon described [16,

256 45], as higher muscle glycogen at the onset of exercise results in accelerated glycogen usage

257 thereby producing similar muscle glycogen concentrations at the end of exercise [35].

258 Supporting this, whole-body carbohydrate balance was higher when breakfast was consumed

259 at the onset of exercise, but did not differ between breakfast and fasted trials following

260 exercise, due to greater rates of carbohydrate utilization [45].

261

262 Liver glycogen content is more likely to play a role in the post-exercise second-meal

263 phenomenon. Liver glycogen concentration is elevated by ~21%, 2 h after consumption of a

264 mixed-macronutrient liquid meal [58]. Liver glycogenolysis is stimulated during exercise in

265 order to maintain blood glucose concentrations [59]. Thus, in the immediate post-exercise

266 period, residual liver glycogenolysis and glucose output could account for an elevated

267 glucose appearance rate. As pre-exercise liver glycogen content positively associates with

268 liver glycogen use during exercise [36], prior meal ingestion and the subsequent elevation of

269 pre-exercise liver glycogen content are likely to accentuate this effect.

270

271 The majority of studies discussed thus far have employed endurance-type exercise that is

272 unlikely to significantly damage muscle. Other types of exercise should be considered,

273 particularly those that involve substantial contributions from eccentric contractions such as

274 downhill running and resistance-type exercise. Eccentric exercise acutely reduces skeletal

275 muscle GLUT4 content, manifesting in insulin resistance at the whole body level [60], and

276 thus the consequences of exercise with an eccentric contractile component may produce a

277 greater reduction in glucose tolerance [61], although some have shown that this is

278 compensated for by greater insulinemia [62].

279

280 Based on the evidence discussed, the mechanisms that underlie the post-exercise increase in

281 postprandial glycemia with prior meal consumption (Figure 4) may involve a combination of

282 increased intestinal absorption (and exogenous glucose appearance), increased hepatic

283 glucose output, decreased insulin sensitivity in non-exercised limbs (and in exercised limbs

284 when muscle damage is inflicted). It should be noted that these are putative reasons that

285 require research to understand the individual contribution of each component. Further work

286 into the impact of the pre-exercise meal composition on the post-exercise second meal

287 phenomenon would be valuable. A suitable starting point could be manipulation of the

288 breakfast glycemic index [63], which is known to influence exercise metabolism [64].

289

290 Crucially, this intriguing immediate post-exercise second-meal phenomenon should be

291 interpreted in the context of more long-term effects of acute and chronic exercise on

292 metabolic function. A single bout of exercise enhances oral glucose tolerance assessed at 24

293 or 72 h post-exercise [41], and exercise training improves insulin sensitivity for up to 60 h

294 after the final exercise bout [65]. Glucose tolerance in response to training is maintained in

295 healthy populations and improved in those with type 2 diabetes (for a review see [66]).

296 Therefore, the decrement in glucose tolerance discussed here is likely constrained to the

297 immediate post-exercise period. Based on evidence where the plasma glucose response to

298 meals of different glycemic indices does not differ immediately post-exercise, but does at 4 h

299 [67], then the time-course for this phenomenon to persist lies between 0 and 4 h post-

300 exercise. The implications that this has for health are not known, although given that rapid

301 replenishment of glycogen stores (which is sometimes encouraged for athletes training

302 multiple times per day) is not necessary for the general population, perhaps less emphasis

303 should be placed on consumption of large quantities of carbohydrate following exercise for

304 the general public.

305

306 **Conclusions**

307 Assessing glycemic responses to food ingestion provides insight into risk of morbidity and

308 mortality. Given that the majority of eating occasions in western society take place whilst still

309 in the postprandial state from the previous meal, it is arguably of greater importance to assess

310 postprandial responses to sequential meal ingestion. This is further highlighted by the

311 improved glucose tolerance in response to a meal consumed in the postprandial vs. the fasted

312 state, first observed almost 100 y ago. Since then, a number of mechanisms have been

313 revealed that underlie this effect known as the second-meal phenomenon. These include

Page 13

314   delayed gastric emptying, enhanced GLP-1 concentrations, potentiation of early phase insulin

315   secretion, suppression of hepatic glucose output and enhanced muscle glucose uptake. More

316   recently a paradoxical post-exercise second-meal phenomenon has been observed, whereby

317   glucose tolerance following exercise is worsened by prior meal ingestion. The mechanisms

318   underlying this effect are not yet clear, although they may involve enhancement of intestinal

319   absorption and exogenous glucose appearance, hepatic glycogenolysis and endogenous

320   glucose appearance, perhaps combined with reduced insulin sensitivity of non-exercised and

321   damaged muscle, which partially offset the contraction-induced insulin sensitivity in

322   exercised (non-damaged) muscle.

323

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509 **Figure Legends**
510

511 **Figure 1** Mechanisms underlying the second-meal phenomenon at rest. Prior exposure to a
512 meal delays gastric emptying of a subsequent meal with concomitant increases in GLP-1
513 concentrations. This likely reduces exogenous glucose appearance and splanchnic glucose
514 output. Potentiation of early phase insulin secretion is due to prior insulin secretion in concert
515 with reduced NEFA exposure and enhanced GLP-1 concentrations. Reduced NEFA exposure
516 also likely contributes to the reduction in hepatic glucose output and enhanced insulin
517 sensitivity and muscle glucose uptake. GLP-1, glucagon-like peptide-1; NEFA, non-esterified
518 fatty acids. Lines with arrows represent pathways of stimulation; Lines with filled circles
519 represent pathways of inhibition.
520

521

522 **Figure 2** Blood glucose response to FR, BR, FE and BE trials. (a) blood glucose
523 concentration. FR, fasted rest; BR, breakfast rest; FE, fasted exercise; BE, breakfast exercise
524 trials; BL, baseline; PE, pre-exercise; EX; exercise; a, FR different to BR; b, FR different to
525 FE; c, FR different to BE; d, BR different to FE; e, BR different to BE; f, FE different to BE
526 ($P < 0.05$). (b) time-averaged blood glucose area under the curve following test-drink
527 consumption. Bars not sharing a common superscript letter are significantly different from
528 one another ($P < 0.05$). $n = 11$. Figure reproduced from Gonzalez *et al.* [48].
529

530 **Figure 3** Serum insulin response to FR, BR, FE and BE trials. (a) serum insulin
531 concentrations. FR, fasted rest; BR, breakfast rest; FE, fasted exercise; BE, breakfast exercise
532 trials; BL, baseline; PE, pre-exercise; EX; exercise; a, FR different to BR; b, FR different to
533 FE; c, FR different to BE; d, BR different to FE; e, BR different to BE; f, FE different to BE
534 ($P < 0.05$). (b) time-averaged serum insulin area under the curve following test-drink
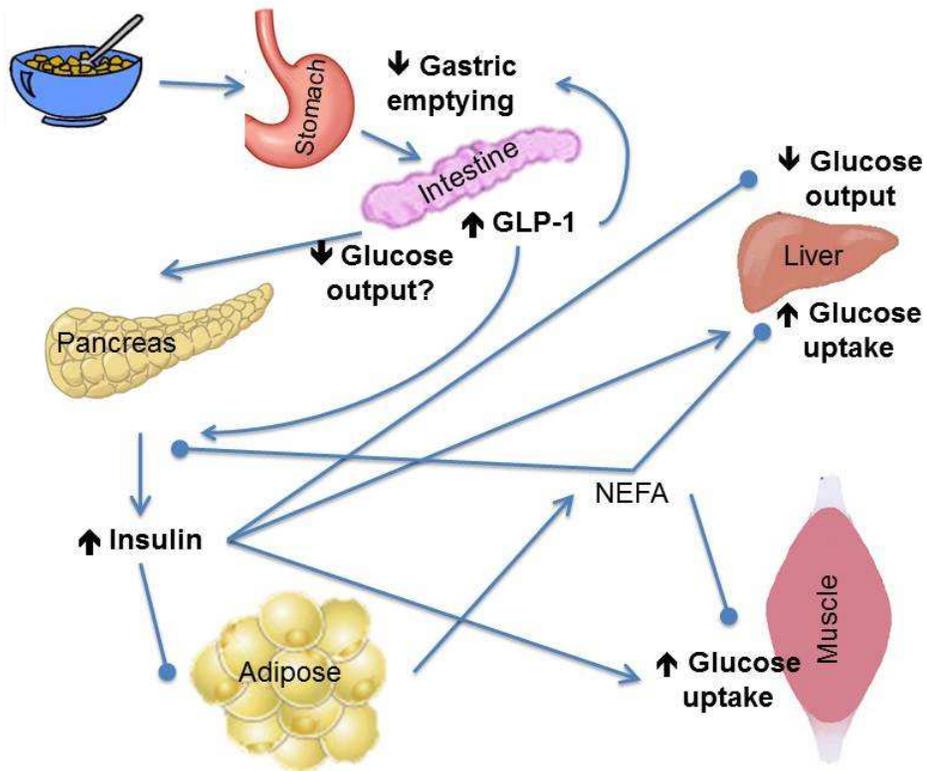535 consumption. $n = 11$. Figure reproduced from Gonzalez *et al.* [48].
536

537 **Figure 4** Mechanisms underlying the paradoxical second-meal phenomenon in the immediate
538 post-exercise period. Exercise increases intestinal absorption and splanchnic glucose output,
539 potentially exasperated by food present in the gastrointestinal tract. A higher pre-exercise
540 liver glycogen content from a prior meal may enhance hepatic glycogenolysis and thus
541 hepatic glucose output. Muscle contraction will increase glucose uptake in the active muscle,
542 but may be somewhat counteracted by EIMD and insulin resistance in non-exercised muscle
543 from elevated NEFA exposure and lipid accumulation during exercise. EIMD, exercise-
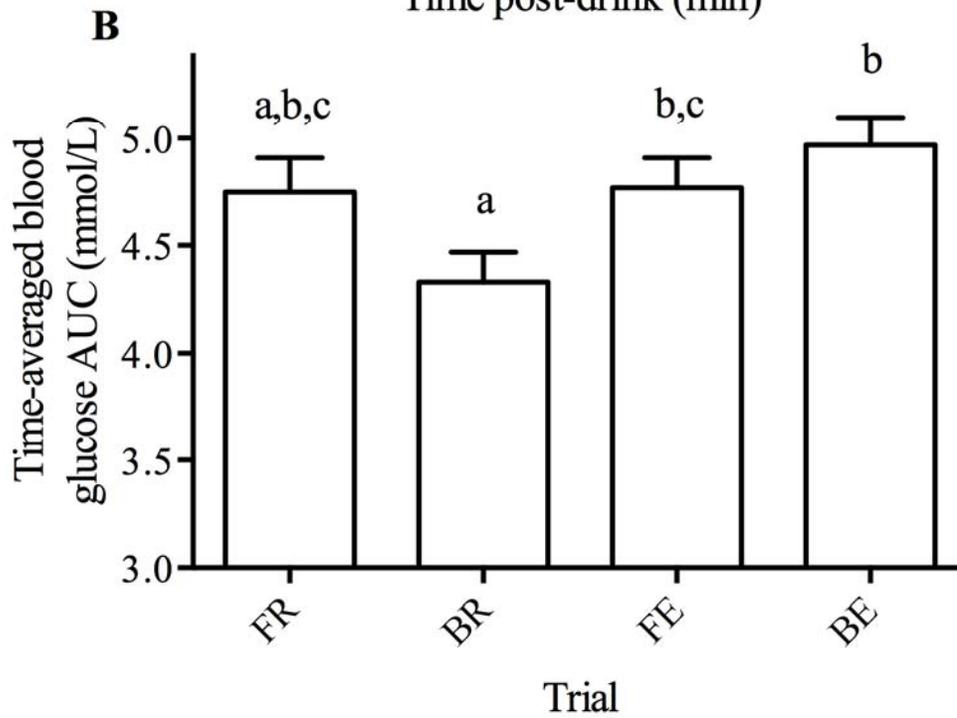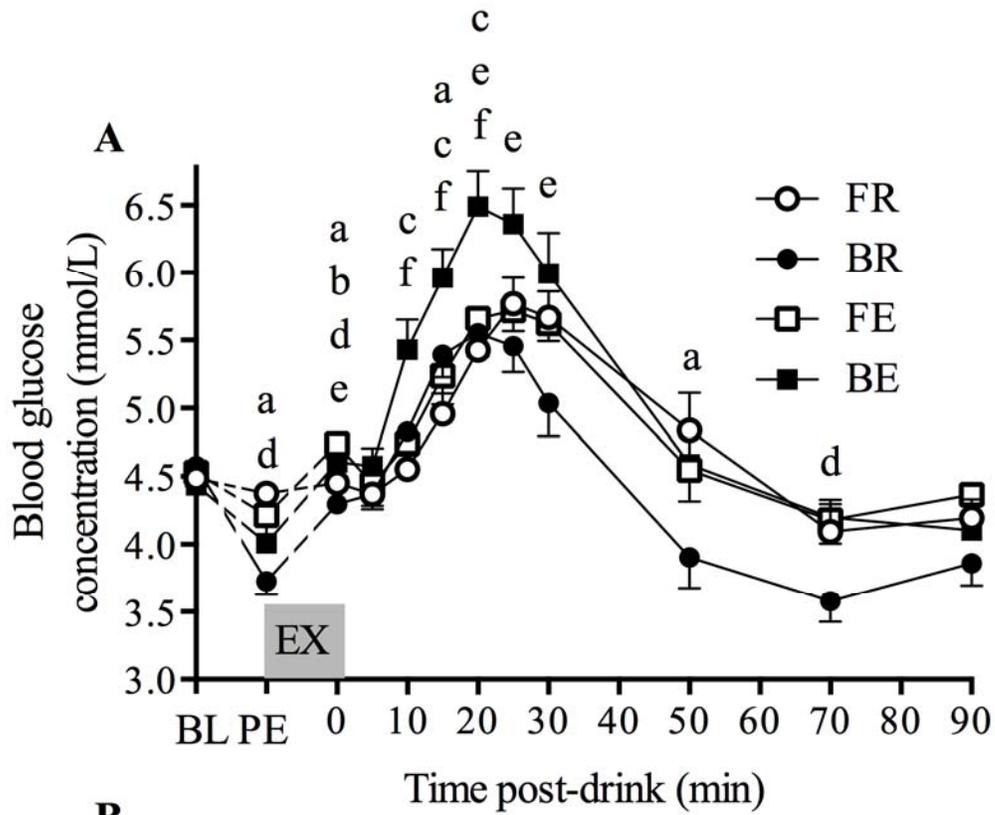544 induced muscle damage; NEFA, non-esterified fatty acids.
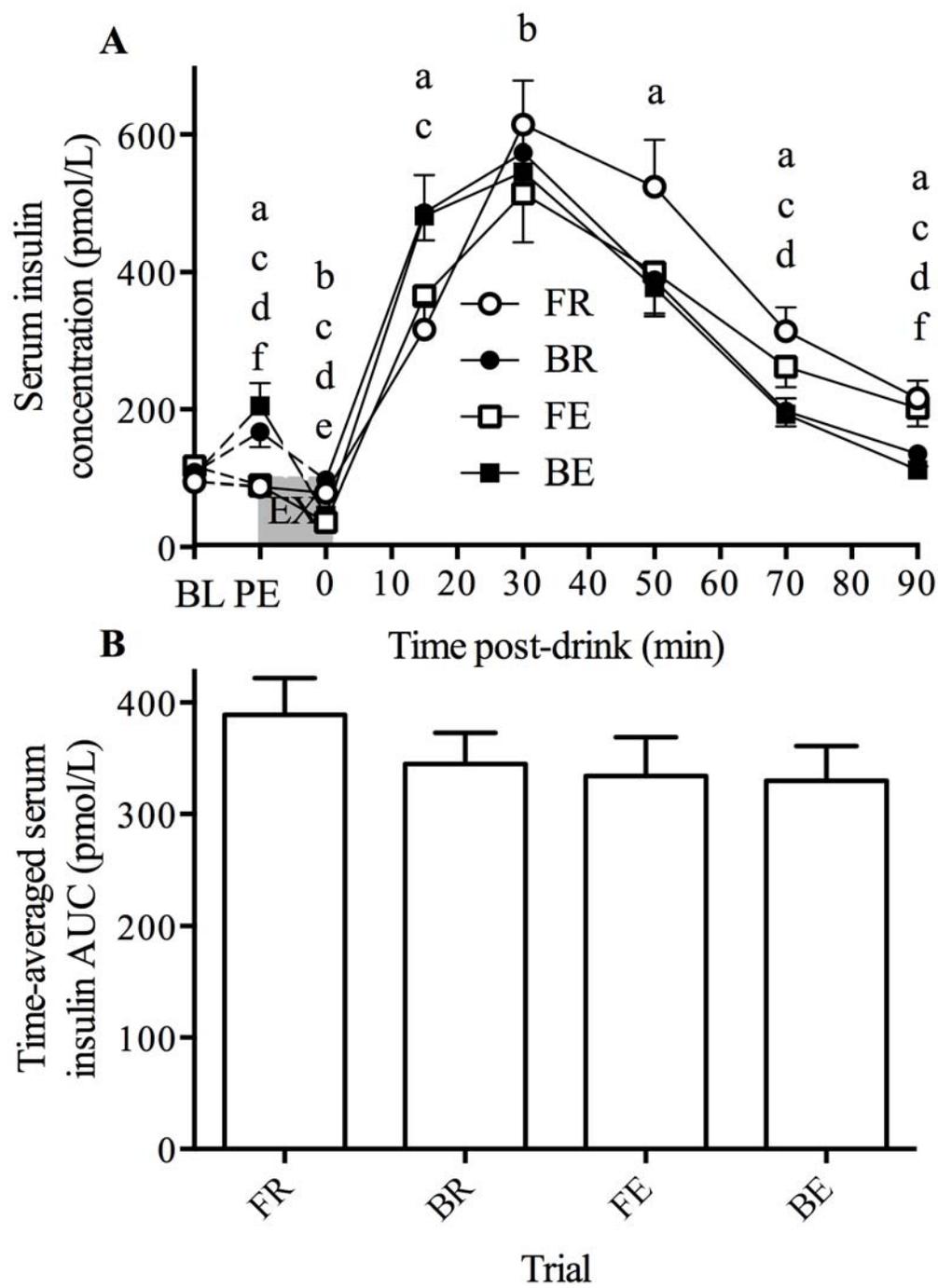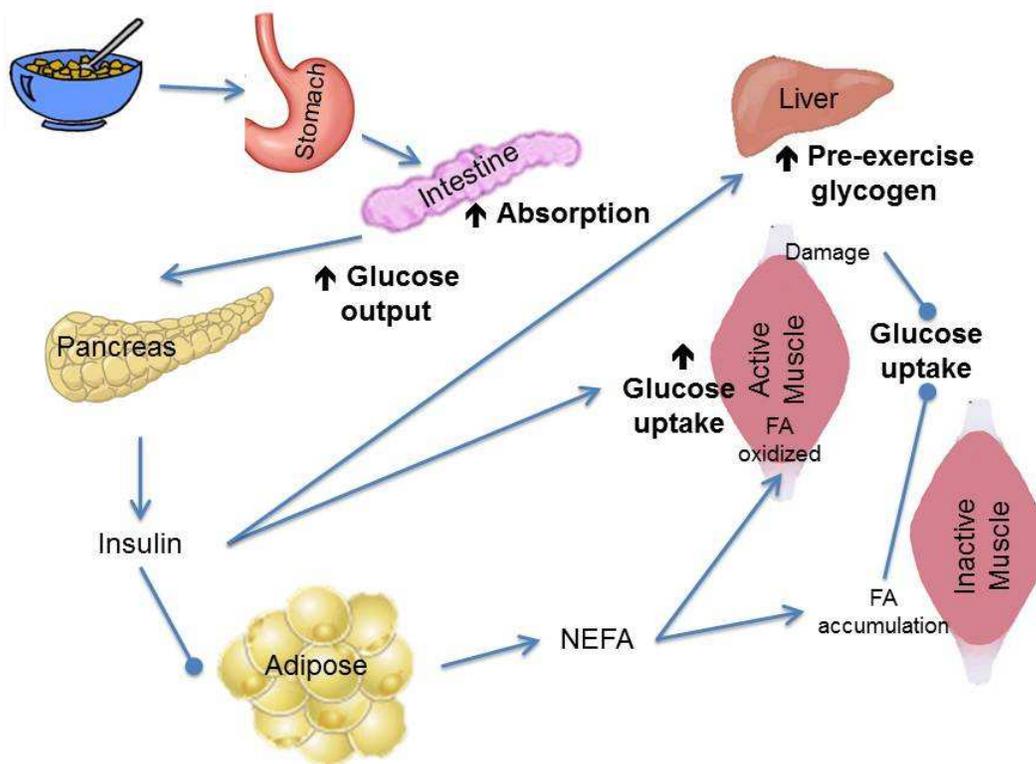545
546
547
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A

Serum insulin concentration (pmol/L)

- FR
- BR
- FE
- BE

EX

Time post-drink (min)

BL PE 0 10 20 30 40 50 60 70 80 90

B

Time-averaged serum insulin AUC (pmol/L)

FR BR FE BE

Trial