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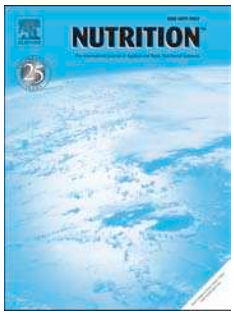

Paradoxical second-meal phenomenon in the acute post-exercise period

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Abstract

Attenuating blood glucose excursions in the postprandial state has the capacity to reduce the risk of cardiovascular disease, type 2 diabetes and mortality, even in apparently healthy populations. Almost a century ago it was reported that oral glucose tolerance is improved by prior glucose consumption. This was termed the second-meal phenomenon and is also seen with consumption of mixed-macronutrient containing meals. In this context a number of mechanisms probably contribute to the attenuation of glycemia, including: gastric emptying, early-phase insulin secretion, hepatic glucose output and muscle glucose uptake. More recently, a paradoxical second-meal phenomenon has been observed in the immediate post-exercise period whereby prior meal consumption deteriorated glucose tolerance. The mechanisms regulating the post-exercise second-meal phenomenon are less clear, but are likely to involve an increase in intestinal absorption, greater hepatic glucose output, and under circumstances of muscle-damage, reductions in muscle glucose uptake. Further work is required to confirm these mediating factors and to characterize the time-course of this paradox, which is likely to only exist within the first 4 h following exercise. Critically, this acute post-exercise phenomenon should be maintained in the perspective of the benefits of chronic exercise training, which for the majority of individuals improves glycemic control and reduces many health risks including those associated with exaggerated postprandial glycemia.

Key words: exercise, fatty acids, glucose, insulin, metabolism, postprandial, type 2 diabetes.

Introduction

Investigating glycemic responses to food ingestion is pertinent to all individuals due to the strong links that glucose tolerance has with cardiovascular disease (CVD), type 2 diabetes and mortality [1]. Even in populations considered healthy (fasting and 2 h postprandial glucose < 6.1 and < 7.8 mmol/L, respectively), those with higher postprandial glucose concentrations relative to fasting, have a ~10-20% increased risk of heart disease or stroke [2]. Accordingly, studying glucose tolerance is appropriate to all individuals across the metabolic health spectrum, from those with diagnosed type 2 diabetes, to those with impaired, and normal, glucose tolerance. That postprandial glycemia is more strongly associated with mortality than fasting glycemia reflects the relative importance of this measure. This review discusses mechanisms underlying a well-established postprandial glycemic effect seen in response to sequential meals known as the second-meal phenomenon, and proceeds to describe a more recent paradoxical second-meal phenomenon, revealed in the immediate post-exercise period.

Regulation of blood glucose homeostasis

Before interventions are discussed, the regulation blood glucose concentration will be briefly reviewed. Circulating glucose concentrations represent the dynamic balance between endogenous glucose appearance (from hepatic glycogenolysis and gluconeogenesis), exogenous glucose appearance (via the intestine), and glucose disappearance (into tissues). After an overnight fast, the amount of glucose in circulation is fairly constant at ~4.6 g in an 80 kg individual [3]. Hypothetically, if no regulatory mechanisms existed, it has been calculated that the carbohydrate content of a typical meal would raise blood glucose

concentration more than 8-fold [4]. However, at least in healthy people, synchronized regulation means that blood glucose concentration rises to ~60% above its fasting value [4]. The regulation of blood glucose concentration in response to carbohydrate ingestion transpires at a number of levels including: gastric emptying, intestinal absorption, splanchnic and peripheral perfusion, and rates of tissue glucose uptake, which are all under some hormonal control.

A hormone of great importance in glycemia is insulin, which reduces blood glucose concentrations by suppressing hepatic glucose output [5] and stimulating muscle (and to lesser degrees hepatic and adipose) glucose uptake. Insulin-induces translocation of the glucose transporter isoform 4 (GLUT4) to the cell membrane surface (in the absence of insulin, ~90% remain in intracellular vesicles [6]), allowing more glucose to enter the cell [7]. Muscle is the tissue of greatest significance with regards to postprandial glucose uptake, responsible for up to 90% of glucose disposal [8].

Gastrointestinally-derived hormones also make important contributions. Namely, glucose-dependent insulinotropic peptide (formerly known as gastric inhibitory polypeptide; GIP) and glucagon-like peptide-1 (GLP-1). Enteroendocrine cells in the intestine secrete these peptides in response to nutrient exposure [9-11] and both these peptides potently stimulate insulin secretion [12]. Thus, oral ingestion of food produces divergent insulin secretory and sensitivity responses compared to intravenous glucose infusions, as direct contact of nutrients with intestinal cells influences insulin secretion and action [13, 14]. Thereby having obvious implications for interpreting studies using intravenous methods of glucose delivery and oral glucose tolerance tests (OGTT) using glucose only.

The second-meal phenomenon

Western eating patterns typically result in the consumption of at least 3 meals per day [15]. With this in mind, studying responses to sequential food intake (as opposed to single meals) is vital to translate laboratory findings into daily life [16]. Sequential OGTTs led to the discovery of the second-meal phenomenon, which describes the improved glucose tolerance seen after consumption of a prior glucose load. This was first observed in 1919 [17] and was subsequently replicated [18] and termed the "Staub-Traugott" effect.

This effect is evident in those with and without type 2 diabetes [19-21] and in response to intravenous glucose infusion [22]. Most relevant for practical application, is that this response is seen with mixed-macronutrient meals [21, 23]. The efficacy of the response to sequential-meals is dependent on the composition of the prior meal. For instance, a moderately fatty breakfast tends to increase the glucose area under the curve (AUC) in response to a standard lunch ($P = 0.08$), and is significantly higher than after a low-fat breakfast ($P = 0.03$) [24]. This effect is also detectable in OGTT performed in the morning, with macronutrient manipulation of an evening meal [25]. A higher glycemic index (GI) and/or lower fermentable carbohydrate content of a prior meal can also increase the glycemic response to a second, standard meal [26]. The mechanisms that underlie the second-meal phenomenon at rest likely involve a combination of delayed gastric emptying, enhanced insulin secretion, suppression of hepatic glucose production and enhanced muscle glucose uptake (Figure 1).

Prior consumption of fat or protein slows gastric emptying of a subsequent carbohydrate-rich meal, doubling the time to clear 50% of stomach content (known as T50 [19, 27]). Both these studies also found greater postprandial responses of plasma GLP-1 [19, 27], which slows gastric emptying [28] and potentiates insulin secretion [12].

Potentiated early-phase insulinemia following sequential meals is apparent [29] and is likely due to priming of pancreatic β-cells by prior insulin exposure, along with suppressed pancreatic NEFA exposure and increased GLP-1 concentrations. Evidence for these mechanisms is provided by the potentiation of insulin secretion (by 32%) in response to intravenous glucose with prior insulin infusion. Furthermore, insulin potentiation is somewhat preserved (but attenuated to a 20% increase) when intralipid-heparin is co-infused to maintain high NEFA concentrations [30]. This eliminates confounding from prolonged (>6 h) fatty acid exposure to β-cells, which inhibits pancreatic insulin secretion [31].

Bonnucelli *et al*. employed triple tracer techniques to reveal glucose kinetics during sequential glucose ingestion (separated by 180 min) [32]. A suppression of endogenous glucose production along with insulin potentiation, almost entirely accounted for the second-meal effect observed in this study. Neither exogenous glucose appearance rates, nor glucose disappearance rates were influenced. This contrasts with other work showing that oral glucose loads (of either 15 or 25 g) delivered ~100 min prior to a euglycaemic, hyperinsulinaemic clamp improve whole-body insulin sensitivity, as evidenced by a ~40% greater glucose infusion rate [33]. This is also supported by the evidence of greater muscle glycogen storage with the second-meal effect, in the presence of comparable insulinemia [21]. The discrepancies between Bonnucelli *et al.* [32] and those showing delayed gastric

emptying (thus influencing exogenous appearance [19, 27]) and enhanced glucose disappearance rate [21, 22, 33] can be explained by additional nutrients, and the time-delay between sequential ingestive events.

Glucose tolerance is improved with the ingestion of sequential meals. This is likely due to a combination of factors including slower gastric emptying (slowing exogenous glucose appearance), combined with increased early-phase insulin secretion, reduced endogenous glucose output from the liver, and enhanced glucose clearance by muscle (Figure 1).

Post-exercise glucose tolerance

Exercise produces large changes in substrate fluxes, dependent on intensity and duration of exercise. Carbohydrates provide a major contribution to energy expenditure during moderate-intense endurance exercise in the forms of muscle glycogen and plasma glucose [34]. Accordingly, 30 min of treadmill running at 70% $\dot{V}O_2$max (maximal oxygen consumption) depletes muscle glycogen by ~30% [35]. Insights gained from ^{13}C nuclear magnetic resonance spectroscopy reveal that 90 min of cycling [at 70% $\dot{V}O_2$peak (peak oxygen consumption)] reduces muscle and hepatic glycogen reserves by ~60% and ~40%, respectively [36]. The drive to replenish glycogen depots post-exercise leads changes in muscle and liver metabolism that have consequences for postprandial glucose kinetics.

It is well-established that exercise increases muscle glucose uptake independent of insulin (for a recent comprehensive review see Richter and Hargreaves [37]). Muscle insulin sensitivity is also improved, which persist following full glycogen replenishment [38], suggesting the drive to replenish glycogen is not the only explanation for post-exercise

insulin sensitivity enhancement. Elevated post-exercise muscle glucose uptake makes it attractive to speculate that oral glucose tolerance would also be improved; however this is not always the case. Acute endurance-type exercise tends to deteriorate [39-42], or not significantly affect [43, 44] oral glucose tolerance in healthy people. Differences between studies, such as the nutritional status of participants prior to the exercise bout (fasted/fed), and the time delay between exercise and glucose tolerance assessment, may contribute to the equivocality. A recent study addressed the issue of nutritional status by evaluating the response to consumption of a mixed-macronutrient beverage (16 g protein, 56 g carbohydrate and 8 g fat) following exercise in the fasted and fed state [45]. Healthy males completed 4 trials in a randomized, crossover design. Trials consisted of a fasted rest trial (FR) a breakfast rest trial (BR), a fasted exercise trial (FE) and a breakfast exercise trial (BE). The porridge-based breakfast (19 g protein, 67 g carbohydrate and 11 g fat) was provided 2 h prior to exercise, which comprised treadmill running at 60% $\dot{V}O_2$peak for ~60 min (until 2.9 MJ had been expended). In the fasted state, glucose tolerance was similar between exercise and rest trials supporting some previous findings. Following breakfast consumption however, exercise produced a surprising 15% *increase* in the blood glucose AUC, relative to rest (Figure 2; P = 0.012). Peak blood glucose concentrations were also greater (~16%; P = 0.03) in the BE trial compared to BR. This post-exercise effect is somewhat enigmatic on first impression and provokes an interesting discussion into the ostensible mechanisms that underlie this paradoxical phenomenon. One interesting point is that impaired glucose tolerance was present even though there was apparent potentiation of early phase insulin secretion, as indicated by the significantly higher serum insulin concentrations 15 min post-drink consumption in BR and BE trials (Figure 3).

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

Cycling exercise (using predominantly lower-limb musculature) does not influence basal glucose uptake in the forearm (comprising non-exercised muscle), and insulin-stimulated glucose uptake is in fact *impaired* [46]. This may be due to intramuscular lipid accumulation [47] from high NEFA exposure and low lipid utilization during exercise. Therefore the impact of exercise on whole-body glucose disposal is dependent on recruitment of large muscle groups, with non-exercised muscle in fact dampening the enhancement of whole-body insulin sensitivity produced by exercised muscle. Notwithstanding this, whole-body glucose uptake is enhanced after endurance exercise in the fasted state [42]. Whether consumption of a meal, prior to exercise, influences lipid accumulation and subsequent insulin resistance in non-exercised muscle remains to be determined. Moreover, tracer studies in both canines [48] and humans [42], indicate a larger role of increased glucose appearance in influencing oral glucose tolerance.

Rose *et al*. demonstrated that postprandial whole-body glucose disappearance is enhanced by 24% when exercise precedes an OGTT [42]. This was however, completely superseded by a 30% elevation in the glucose appearance, which was primarily due to exogenous (orally-derived) glucose appearance, although endogenous glucose appearance (hepatically-derived), was also higher following exercise. Changes in gastric emptying rates are not evident post-exercise at the intensities used in the studies described [49, 50], leaving perfusion and/or intestinal permeability to explain the greater rates of exogenous glucose appearance. Intestinal perfusion positively associates with intestinal glucose absorption [51] and exercise increases subsequent postprandial splanchnic perfusion by 15-35% [52]. Moreover, food consumption prior to exercise increases splanchnic perfusion during exercise [49], providing

a possible avenue through which prior nutritional status influences glucose tolerance in the post-exercise period. Although, using arterial-venous difference and tracer techniques in dogs, it was shown that intestinal glucose absorption is enhanced following exercise, in spite of the absence of a significant change in splanchnic perfusion [48]. Therefore it remains inconclusive as to whether changes in blood flow contribute to the post-exercise second-meal phenomenon in humans, leaving an elevated intestinal absorption rate as a probable mediator.

Increased exogenous glucose appearance could also be due to intestinal barrier dysfunction. Cycling (70% maximum power output) for 60 min increases small intestine permeability [53], with evidence of intestinal cell damage (indicated by elevated circulating concentrations of intestinal fatty acid binding protein) which positively correlate with the degree of splanchnic hypoperfusion. These findings suggest that in fact a reduction in splanchnic perfusion is responsible for intestinal damage and permeability to carbohydrates, which contradicts the previous discussion regarding splanchnic perfusion. However, reduced splanchnic blood flow is only pertinent to high-intensity exercise, as no hypoperfusion is evident at 55% $\dot{V}O_2$peak [49].

There are other candidates for inducing intestinal glucose absorption and/or permeability following lower intensity exercise. These include heat [54] and hormonal changes involving epinephrine [55, 56] and vasoactive intestinal peptide [40]. Regarding diet, intake of fiber, fat, protein and drinks of high-osmolality are associated with self-reported gastrointestinal distress during triathlon [57]. Thus, gastrointestinal damage may occur from mechanical stress, particularly during running, potentially exasperated by the presence of food in the gastrointestinal tract.

Regardless of mechanisms and consequences for glucose tolerance, the accelerated exogenous glucose appearance following exercise could be viewed as advantageous in assisting (along with muscle GLUT4 translocation and glycogen synthase activity) rapid muscle glycogen replenishment post-exercise. Indeed, moderate-intensity (~60% $\dot{V}O_2$max) exercise prior to consumption of high-carbohydrate meals increases postprandial glycemia and enhances glycogen storage and balance [39].

Muscle glycogen is thought to regulate glucose uptake in part, by inhibiting GLUT4 translocation and/or hexokinase activity from glycogenolysis-induced elevations in intramuscular glucose-6-phosphate concentrations [37]. With this in mind, it would seem intuitive that elevated pre-exercise muscle glycogen concentrations (from prior meal consumption) may persist following exercise and contribute to lower glucose uptake relative to fasted exercise. This is however, unlikely to be the case in the phenomenon described [16, 45], as higher muscle glycogen at the onset of exercise results in accelerated glycogen usage thereby producing similar muscle glycogen concentrations at the end of exercise [35]. Supporting this, whole-body carbohydrate balance was higher when breakfast was consumed at the onset of exercise, but did not differ between breakfast and fasted trials following exercise, due to greater rates of carbohydrate utilization [45].

Liver glycogen content is more likely to play a role in the post-exercise second-meal phenomenon. Liver glycogen concentration is elevated by ~21%, 2 h after consumption of a mixed-macronutrient liquid meal [58]. Liver glycogenolysis is stimulated during exercise in order to maintain blood glucose concentrations [59]. Thus, in the immediate post-exercise

period, residual liver glycogenolysis and glucose output could account for an elevated glucose appearance rate. As pre-exercise liver glycogen content positively associates with liver glycogen use during exercise [36], prior meal ingestion and the subsequent elevation of pre-exercise liver glycogen content are likely to accentuate this effect.

The majority of studies discussed thus far have employed endurance-type exercise that is unlikely to significantly damage muscle. Other types of exercise should be considered, particularly those that involve substantial contributions from eccentric contractions such as downhill running and resistance-type exercise. Eccentric exercise acutely reduces skeletal muscle GLUT4 content, manifesting in insulin resistance at the whole body level [60], and thus the consequences of exercise with an eccentric contractile component may produce a greater reduction in glucose tolerance [61], although some have shown that this is compensated for by greater insulinemia [62].

Based on the evidence discussed, the mechanisms that underlie the post-exercise increase in postprandial glycemia with prior meal consumption (Figure 4) may involve a combination of increased intestinal absorption (and exogenous glucose appearance), increased hepatic glucose output, decreased insulin sensitivity in non-exercised limbs (and in exercised limbs when muscle damage is inflicted). It should be noted that these are putative reasons that require research to understand the individual contribution of each component. Further work into the impact of the pre-exercise meal composition on the post-exercise second meal phenomenon would be valuable. A suitable starting point could be manipulation of the breakfast glycemic index [63], which is known to influence exercise metabolism [64].

Crucially, this intriguing immediate post-exercise second-meal phenomenon should be interpreted in the context of more long-term effects of acute and chronic exercise on metabolic function. A single bout of exercise enhances oral glucose tolerance assessed at 24 or 72 h post-exercise [41], and exercise training improves insulin sensitivity for up to 60 h after the final exercise bout [65]. Glucose tolerance in response to training is maintained in healthy populations and improved in those with type 2 diabetes (for a review see [66]). Therefore, the decrement in glucose tolerance discussed here is likely constrained to the immediate post-exercise period. Based on evidence where the plasma glucose response to meals of different glycemic indices does not differ immediately post-exercise, but does at 4 h [67], then the time-course for this phenomenon to persist lies between 0 and 4 h post-exercise. The implications that this has for health are not known, although given that rapid replenishment of glycogen stores (which is sometimes encouraged for athletes training multiple times per day) is not necessary for the general population, perhaps less emphasis should be placed on consumption of large quantities of carbohydrate following exercise for the general public.

Conclusions

Assessing glycemic responses to food ingestion provides insight into risk of morbidity and mortality. Given that the majority of eating occasions in western society take place whilst still in the postprandial state from the previous meal, it is arguably of greater importance to assess postprandial responses to sequential meal ingestion. This is further highlighted by the improved glucose tolerance in response to a meal consumed in the postprandial vs. the fasted state, first observed almost 100 y ago. Since then, a number of mechanisms have been revealed that underlie this effect known as the second-meal phenomenon. These include

delayed gastric emptying, enhanced GLP-1 concentrations, potentiation of early phase insulin secretion, suppression of hepatic glucose output and enhanced muscle glucose uptake. More recently a paradoxical post-exercise second-meal phenomenon has been observed, whereby glucose tolerance following exercise is worsened by prior meal ingestion. The mechanisms underlying this effect are not yet clear, although they may involve enhancement of intestinal absorption and exogenous glucose appearance, hepatic glycogenolysis and endogenous glucose appearance, perhaps combined with reduced insulin sensitivity of non-exercised and damaged muscle, which partially offset the contraction-induced insulin sensitivity in exercised (non-damaged) muscle.

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508

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
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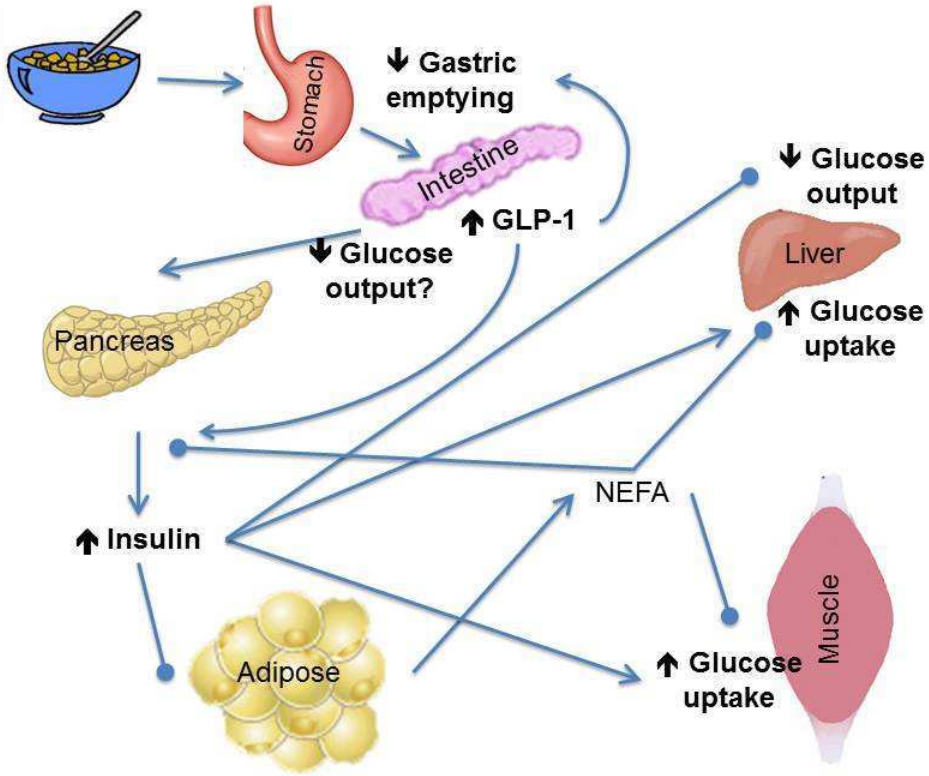
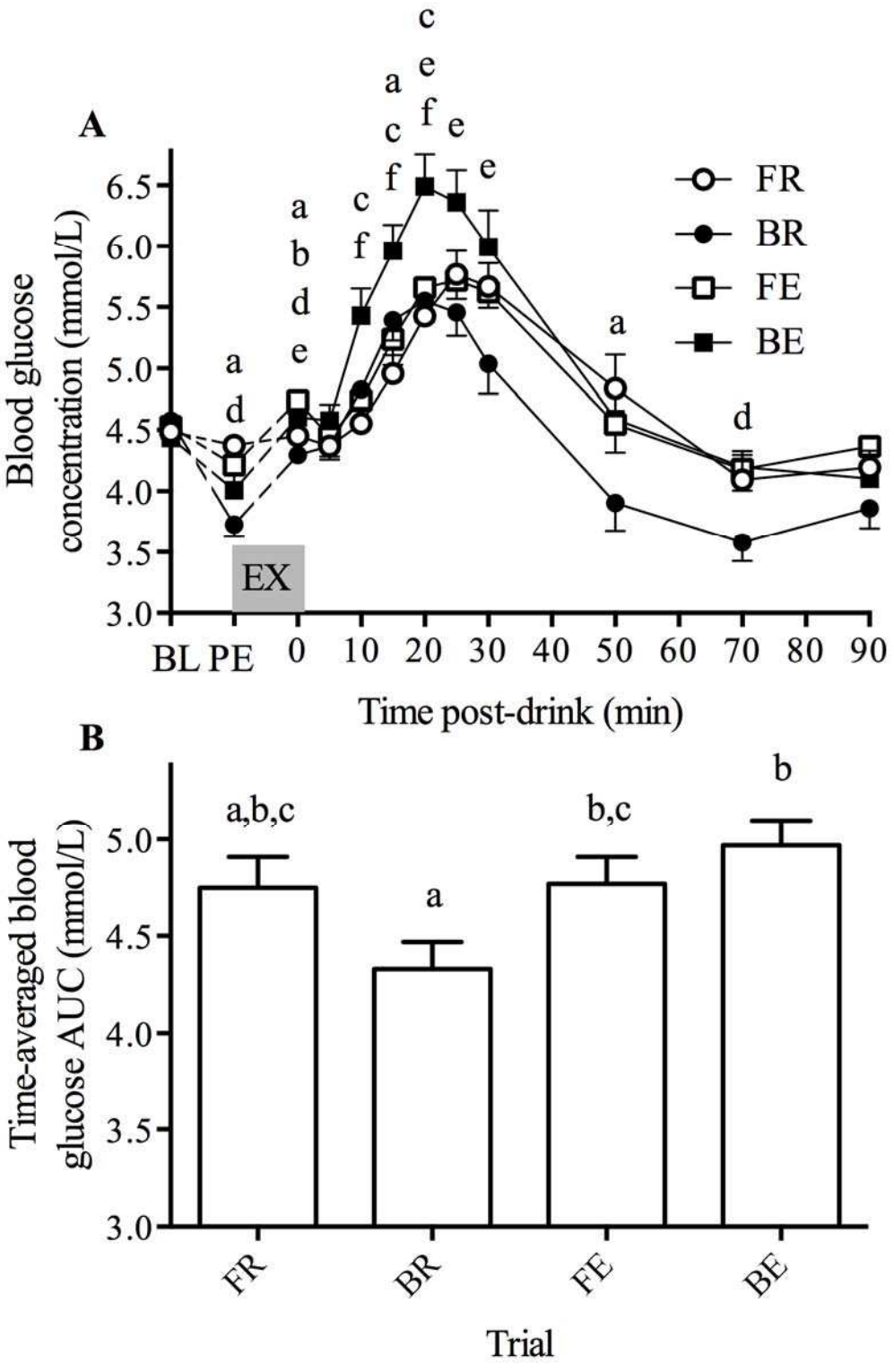
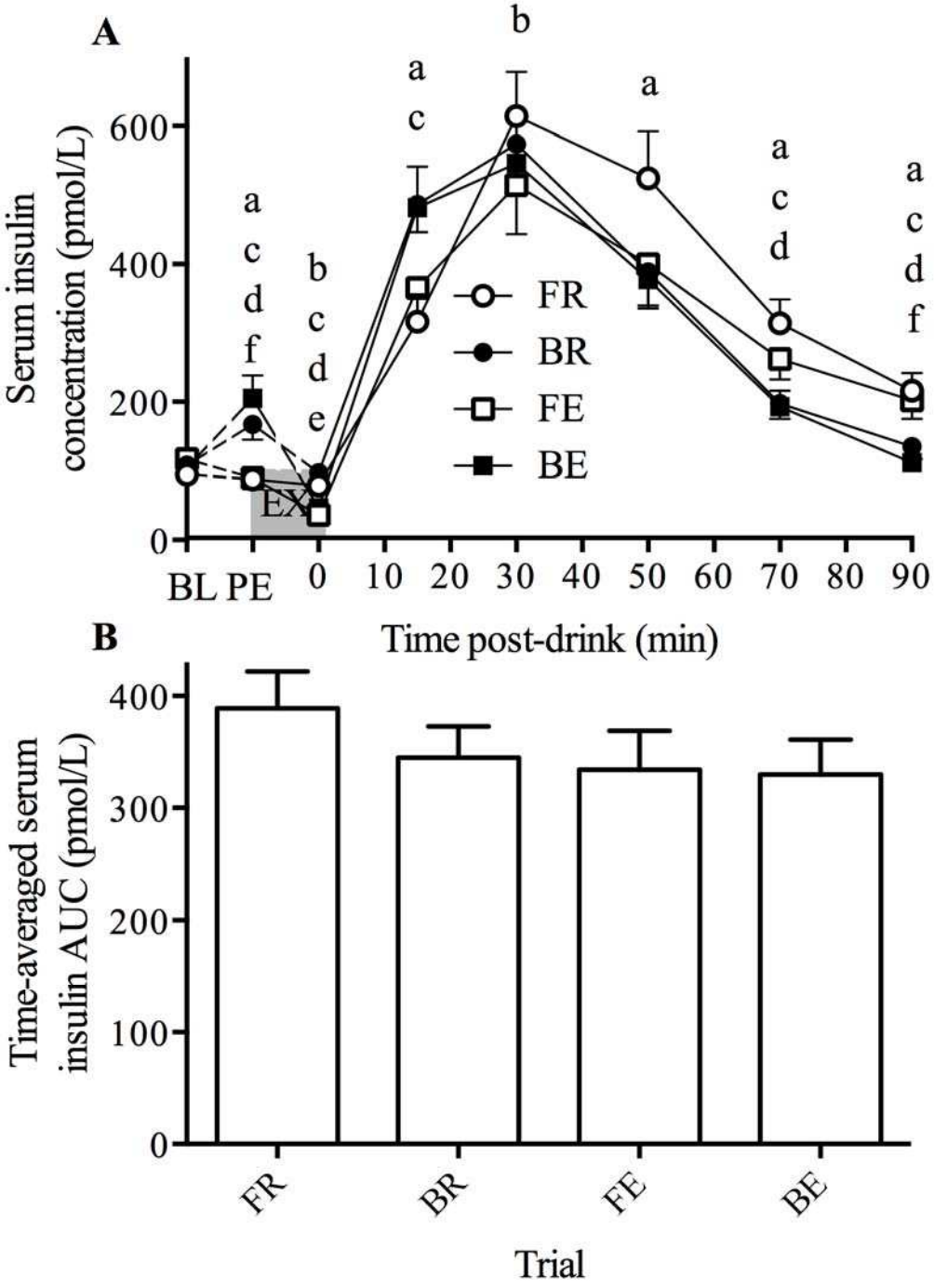
548




A
Blood glucose concentration (mmol/L)
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
FR
BR
FE
BE
EX
BL PE 0 10 20 30 40 50 60 70 80 90
Time post-drink (min)
B
Time-averaged blood glucose AUC (mmol/L)
5.0
4.5
4.0
3.5
3.0
a,b,c
a
b,c
b
FR
BR
FE
BE
Trial


A
Serum insulin concentration (pmol/L)
600
400
200
0
BL PE 0 10 20 30 40 50 60 70 80 90
Time post-drink (min)
FR
BR
FE
BE
EX
a c d f
b c d e
a c
b
a
a c d
a c d f
B
Time-averaged serum insulin AUC (pmol/L)
400
300
200
100
0
FR
BR
FE
BE
Trial