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Review

Paradoxical second-meal phenomenon in the acute postexercise period

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ABSTRACT

Attenuating blood glucose excursions in the postprandial state have the capacity to reduce the risk for cardiovascular disease, type 2 diabetes, and mortality, even in apparently healthy populations. Nearly 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 postexercise period whereby prior meal consumption deteriorated glucose tolerance. The mechanisms regulating the postexercise 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 postexercise 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.

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 an ~10% to 20% increased risk for heart disease or stroke [2]. Accordingly, studying glucose tolerance is appropriate for 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 postexercise period.

Regulation of blood glucose homeostasis

The regulation of blood glucose concentration is briefly reviewed before discussing interventions. 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 eightfold [4]. However, at least in healthy people, synchronized regulation means that blood

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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 hormone 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 regard 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) 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 with IV glucose infusions, as direct contact of nutrients with intestinal cells influences insulin secretion and action [13,14], this has obvious implications for interpreting studies using IV 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 three 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 IV 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 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 OGTTs performed in the morning, with macronutrient manipulation of an evening meal [25]. A higher glycemic index and/or lower fermentable carbohydrate content of a prior meal also can 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 (Fig. 1).

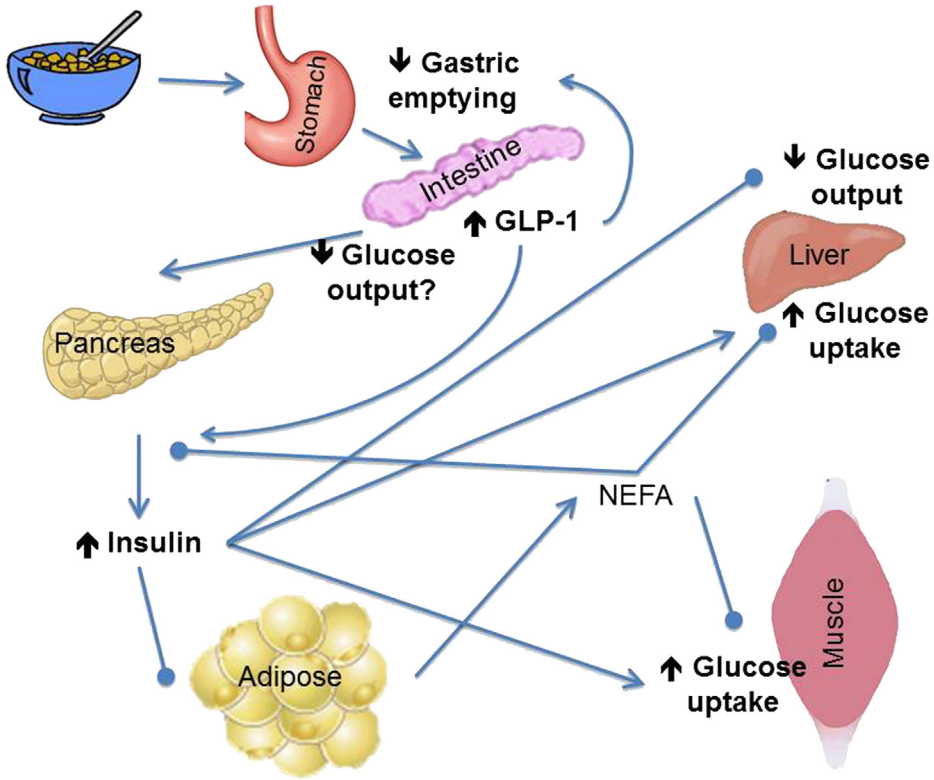

Fig. 1. Mechanisms underlying the second-meal phenomenon at rest. Prior exposure to a meal delays gastric emptying of a subsequent meal with concomitant increases in GLP-1 concentrations. This likely reduces exogenous glucose appearance and splanchnic glucose output. Potentiation of early-phase insulin secretion is caused by prior insulin secretion in concert with reduced NEFA exposure and enhanced GLP-1 concentrations. Reduced NEFA exposure also likely contributes to the reduction in hepatic glucose output and enhanced insulin sensitivity and muscle glucose uptake. Lines with arrows represent pathways of stimulation; lines with filled circles represent pathways of inhibition. GLP-1, glucagon-like peptide-1; NEFA, nonesterified fatty acids.