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Review

Biochemical perspectives on food order: From postprandial glucose control to hormonal modulation

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Abstract

The term "food order" refers to the sequence of nutrient consumption, with a profound impact on metabolic processes, including postprandial blood sugar levels, insulin regulation, and regulation of satiety hormones. In this review, an accent is placed on how meal ordering controls glucose homeostasis and its role in disease prevention, specifically in type 2 diabetes mellitus. Consuming foods high in protein and fiber before carbohydrates is seen to slow gastric emptying and modify hormonal feedback, resulting in reduced glucose and insulin spikes. All these effects occur through several metabolic processes, including glycolysis, gluconeogenesis, AMPK, and mTOR signaling processes. Recognizing these biochemistries highlights food ordering as a potential non-pharmacological intervention for optimizing metabolite function. Individualized nutritional approaches can optimize energy utilization and reduce the need for medication. The long-term benefits and the translation of these approaches for use in diverse groups must be determined in future studies.

Keywords: food order, postprandial glucose, insulin regulation, hormonal signaling, metabolic pathways

Introduction

The order in which macronutrients are consumed, often referred to as the "food order", has received growing attention as a simple yet effective nutritional intervention for promoting metabolic wellness. Recent studies have suggested that both macronutrient timing and sequence can have a profound impact on postprandial blood glucose levels, insulin release, and overall energy metabolism [1, 2]. Specifically, consuming foods high in protein and fiber first, followed by carbohydrates, has been shown to slow gastric emptying and mitigate glycemic spikes following a meal, thereby enhancing insulin sensitivity [3, 4]. These findings suggest that food order could represent a useful non-pharmacological intervention for preventing and controlling metabolic diseases, including type 2 diabetes mellitus (T2DM) [5].

Despite the growing body of work on meal sequencing, significant gaps in current knowledge remain to be addressed. While studies have supported positive acute glycemic improvements, the long-term consequences of food ordering for metabolic wellness and its accompanying biochemistries have yet to be characterized [6]. Specifically, roles for important hormonal regulators, such as insulin and glucagon, as well as incretin hormones like glucagon-like peptide-1 (GLP-1), require additional investigation to understand in detail how these factors contribute to beneficial metabolic consequences when the food intake sequence is manipulated [7].

This review aims to explore the biochemical underpinnings of food sequencing and its impact on blood glucose level regulation and hormonal adaptations. By examining metabolic processes, such as glycolysis, gluconeogenesis, and glycogenolysis, as well as signaling pathways like AMPK and mTOR, this work aims to bridge current gaps in our understanding. Ultimately, a deeper understanding of such processes can enable

personalized nutritional approaches that minimize pharmaceutical intervention and promote sustainable metabolic balance.

Macronutrient metabolism and digestion about food order

Carbohydrates, made up of carbon, hydrogen, and oxygen (1:2:1 ratio), are present as monosaccharides (glucose) or as polymers (starch) [8]. They are initially digested by salivary amylase in the mouth and then by pancreatic amylase in the small intestine, where starch is broken down into disaccharides and ultimately into monosaccharides by brush-border enzymes [9, 10]. Glucose uptake is directed into glycolysis, generating pyruvate and ATP [11]. In excess, it is deposited as glycogen (glycogenesis) in the liver and muscle, and released during starvation through glycogenolysis [12]. The pentose phosphate pathway (PPP) generates ribose-5-phosphate for nucleotides and NADPH for biosynthetic purposes [13]. Glucose homeostasis is ensured by hormonal regulation through insulin (storage) and glucagon (release) (Figure 1) [6].

Proteins with variable R group containing amino acids, polymerize through peptide bonds into functional structures [14]. Protein digestion is initiated by gastric pepsin, followed by pancreatic proteases (trypsin and chymotrypsin) in the intestine, and is finally degraded by brush-border enzymes into absorbable amino acids [15, 16]. Amino acids are utilized for protein synthesis, energy, or metabolite synthesis (for example, gluconeogenesis) (Figure 2) [17, 18]. Transamination and deamination supply nitrogen to the urea cycle and carbon skeletons to the TCA cycle, which has a bearing on the energy balance [18, 19]. Protein consumption regulates gastric emptying and glycemic responses, evincing its function in metabolic control [20, 21].

Lipids, primarily triglycerides (fatty acids combined with glycerol), vary in saturation, resulting in altered physical characteristics [22, 23]. Triglycerides are hydrolyzed by pancreatic lipase, emulsified by intestinal bile acids to monoglycerides and free fatty acids, absorbed by micelles and re-esterified into chylomicrons for lymph transport [24]. Fatty acids are β-oxidized in mitochondria to yield ATP to meet energy demands. Lipids in excess are sequestered in adipose tissue [25].

Food order and postprandial glycemic control

The impact of meal sequencing and dietary fiber on postprandial glucose regulation

Postprandial glucose levels are also influenced by the type of food consumed, as well as the fiber content

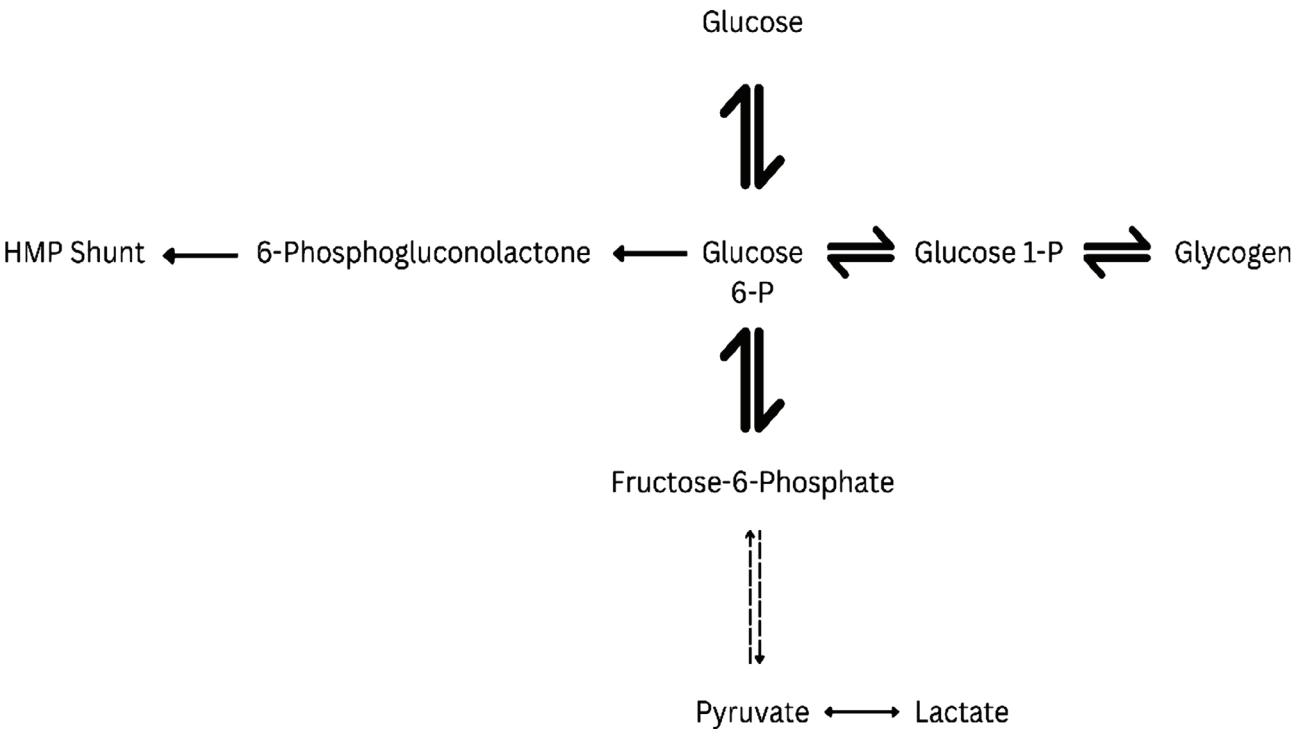

Figure 1: Schematic of glucose metabolism.

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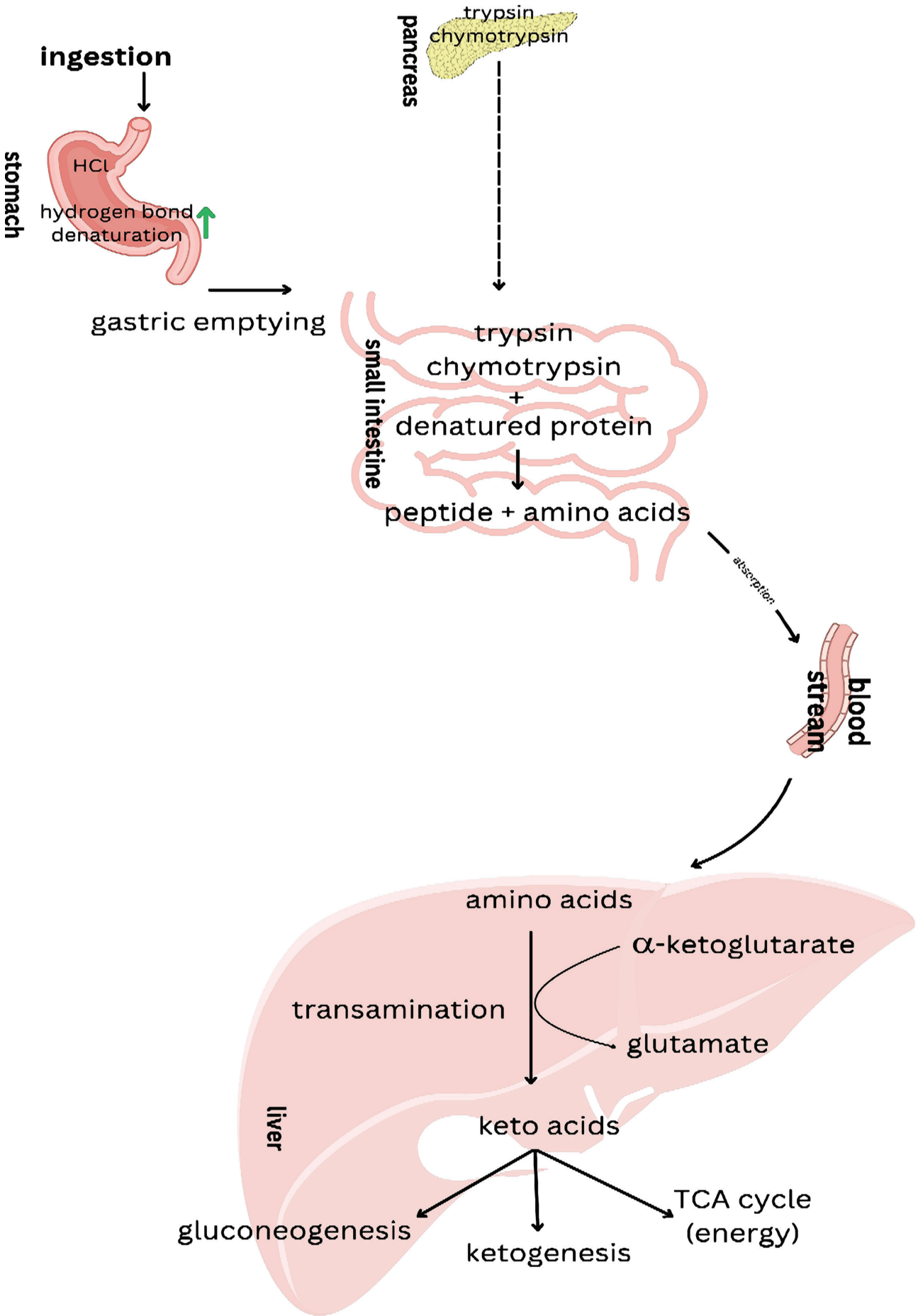

Figure 2: An outline of protein digestion and the metabolism of amino acids.

and total carbohydrate content of the food. Research reveals that consuming foods rich in protein or fat before carbohydrates slows down gastric emptying and thus reduces the acute increase in glucose concentration [3, 26, 27]. On the other hand, consumption of carbohydrates first leads to early absorption of nutrients and subsequent rise in glucose and insulin levels that may lead to insulin resistance in the long run [4]. In addition, the continuative consumption of carbohydrate based meal keeps the incretin hormones (for example, GLP-1, GIP) active and hence improves the sensitivity of insulin and brings the glycemic control to the normal level [5,28]. The body is also made ready to receive the glucose load when protein is introduced shortly before it is required [3].

Vegetables are also a good source of fiber and help regulate glucose levels. Soluble fibers (for example, pectin) form gels that are viscous in the stomach and delay the emptying of the stomach and absorption of carbohydrates; insoluble fibers (for example, cellulose) also slow down the transit time in the intestine so that glucose is released slowly [29, 30]. High fiber diets also lead to fermentation by the colonic microbiota, producing SCFAs, including acetate and butyrate. These SCFAs increase insulin sensitivity, decrease hepatic glucose production, and stimulate GLP-1 secretion, thereby improving glycemic control [31–33] and enhancing intestinal barrier function (Figure 3) [5].

Hormonal regulation of glucose metabolism in relation to food order

How food is consumed affects glucose metabolism through its effects on the hormones. Insulin, produced by the pancreatic β cells, decreases the concentration of blood glucose after a meal by facilitating the uptake of glucose by muscle and adipose tissues, and suppressing the production of glucose by the liver [7]. It has been suggested that a high insulin surge can result from high carbohydrate intake and a high oxidation rate, which may lead to insulin resistance in the long term [34].

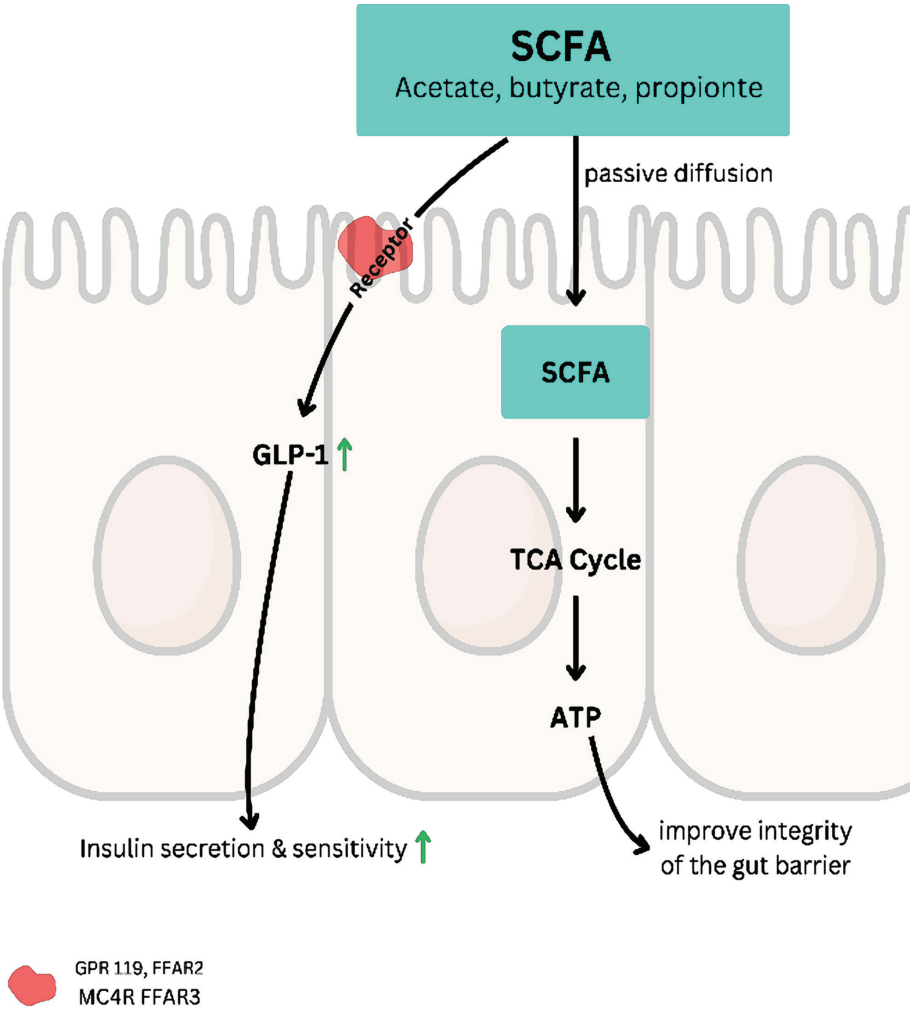

Figure 3: The role of SCA from fibers in enhancing the gut barrier and improving insulin sensitivity and secretion.

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On the other hand, starting a meal with protein or fiber (leafy greens) increases the time of gastric emptying, decreases carbohydrate absorption, and leads to more stable insulin release, which is beneficial for glycemic control [35].

Glucagon, which is secreted by pancreatic α cells, has the opposite effect of insulin; it increases the release of glucose from the liver. Although meals suppress insulin, protein starters can increase glucagon without raising blood glucose, which is beneficial in managing insulin in individuals with insulin resistance [36–38]. Other hormones include the incretin hormones GIP and GLP-1, which control glucose metabolism by increasing insulin secretion in the presence of glucose and suppressing glucagon. Carbohydrates should be consumed during a meal to sustain incretin activity and enhance insulin sensitivity [39–41].

The mechanisms of action of leptin and ghrelin are also involved in regulating metabolic functions. Leptin, secreted by adipocytes, increases the insulin sensitivity and decreases the hepatic glucose production, while ghrelin, secreted by the stomach, increases the appetite and temporarily decreases the insulin level. Notably, meals rich in protein and fiber reduce ghrelin levels, leading to a reduced appetite and stable glucose levels after the meal [21, 42, 43]. Other hormones include cortisol and growth hormone, which elevate the glycemic index through stimulation of gluconeogenesis and insulin resistance [44, 45]. Although stress-related hormonal changes may be continuous, they can be managed through careful planning of meal intake and may have the potential to cure metabolic disorders [46].

Metabolic signaling and implications for "food order"

AMPK signaling pathway

The AMP-activated protein kinase (AMPK) pathway is a central regulator of energy homeostasis that is activated in response to metabolic stress, as indicated by high AMP: ATP and ADP: ATP ratios [47]. Upon activation, AMPK stimulates catabolic pathways that generate ATP while simultaneously inhibiting anabolic processes that consume energy. In the context of food order, initiating a meal with protein followed by carbohydrates can enhance AMPK activation, thereby promoting glucose and fat oxidation while suppressing glycogen synthesis and lipogenesis [48]. This sequence facilitates improved insulin kinetics and more efficient carbohydrate utilization post-meal, contributing to better overall metabolic regulation [20, 21].

m-TOR signaling

The mTOR signaling cascade is a key modulator of cellular metabolism, taking in information from growth factors, amino acids, and glucose to enable both anabolic and catabolic processes [49]. Specifically, mTOR complex 1 (mTORC1) acts as a metabolic rheostat with increased sensitivity to leucine, thereby reflecting the availability of proteins. In terms of nutritional intake, starting meals with high-protein foods maximizes mTORC1 activation, with a rise in both protein synthesis and lipogenesis [36, 50]. In addition, mTORC1 represses autophagy during periods of nutritional abundance, thereby supporting anabolic over catabolic processes. mTORC1 also represses AMP-activated protein kinase (AMPK) directly through phosphorylation, and therefore, enables energy storage in times of nutritional abundance. This double-regulation mechanism ensures that in times of abundant nutrition, mTORC1 promotes anabolic metabolism, while AMPK triggers catabolic processes to generate ATP in times of energy deficiency.

Insulin/PI3K/Akt pathway

The insulin/PI3K/Akt signaling cascade is crucial in linking nutrient perception to regulating cellular energetics. PI3K, in its role of phosphorylating PIP2 to form PIP3, recruits and phosphorylates Akt after insulin binds to its receptor, initiating a cascade of events. Activated Akt facilitates glucose uptake by translocating GLUT4, induces glycogen synthesis through the inhibition of GSK3, and promotes lipogenesis, thereby modulating postprandial blood glucose and fat metabolism. Sequencing food intake—protein or fiber first, then carbohydrates—can mitigate acute blood glucose elevation, improving insulin sensitivity and allowing for a slow and sustained delivery of glucose, which supports Akt-dependent processes [1, 28]. Additionally, this cascade of events communicates with mTOR pathways to modulate anabolic and catabolic processes in a coordinated manner. Importantly, the sequencing of food intake can have a profound impact on metabolic processes and mitigate insulin resistance in obesity and diabetes. In Figure 4, he cascade begins with insulin binding to its receptor, activating PI3K (Phosphatidylinositol 3-kinase), which mediates the conversion of PI-P2 to PI-P3, leading to AKT activation that increases

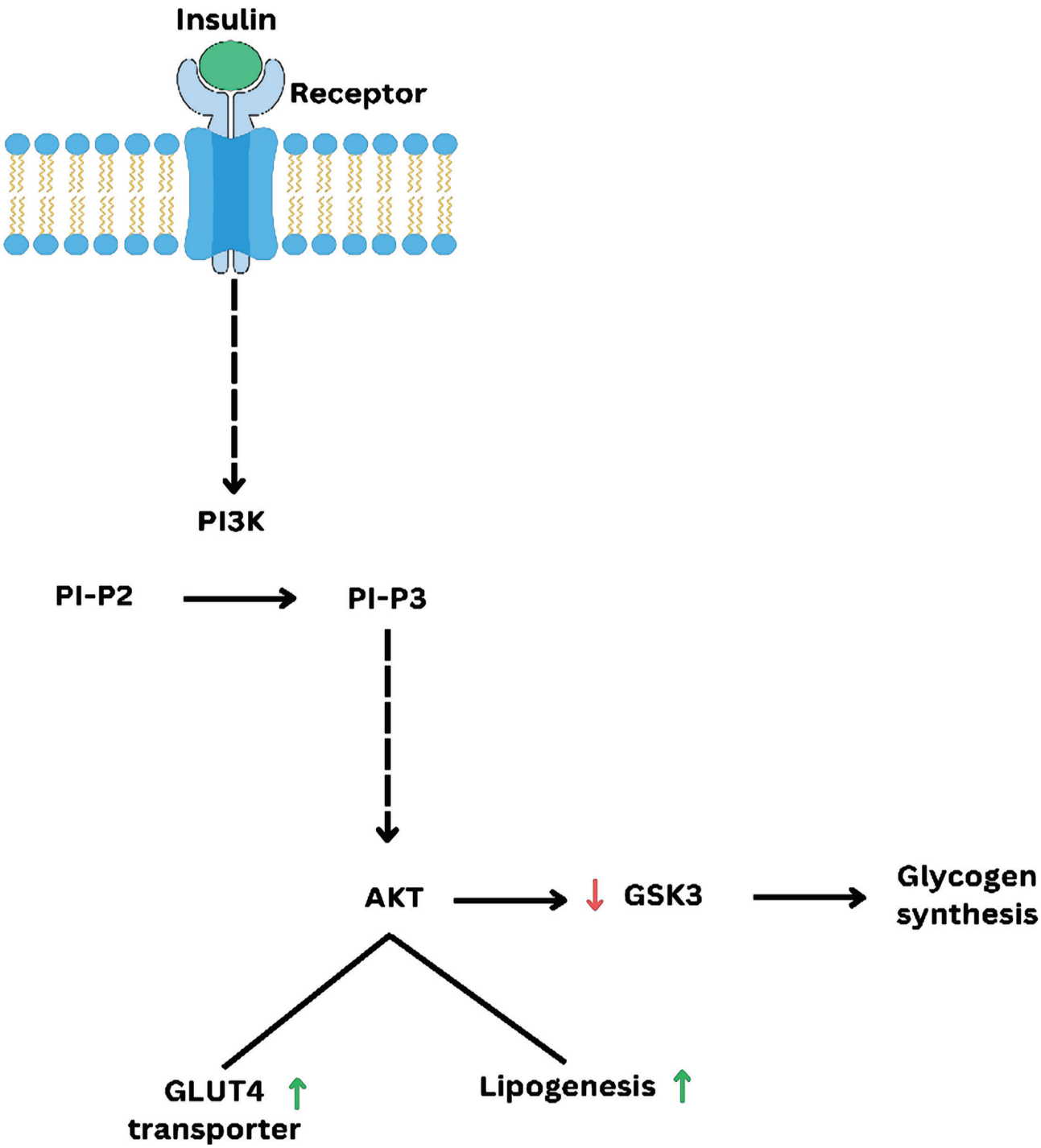

Figure 4: The biochemical process by which insulin affects metabolism.

GLUT4 transporter activity for glucose uptake, enhances lipogenesis (fat synthesis), and inhibits GSK3, resulting in increased glycogen synthesis.

Conclusion

The food consumption pattern holds tremendous potential as a non-pharmacologic intervention for improving metabolic wellness and controlling long-term disease, including type 2 diabetes mellitus. A growing body of work suggests that consuming protein, then fiber, and then carbohydrates in sequence can counteract postprandial hyperglycemia, stabilize insulin and hormonal output, and, in the long run, facilitate optimized glycemic control. Nevertheless, enormous gaps exist in current knowledge about specific biochemical processes, including AMPK- and mTOR-sensitive metabolite-sensitive signaling pathways, which must be addressed in future studies. Future studies should aim

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to understand these processes, establish optimal macronutrient sequencing in various populations, and assess long-term adherence to food sequencing regimens. Overcoming these obstacles could lay the groundwork for personalized nutrition approaches compatible with current nutritional guidance, providing a cost-effective and long-term tool for disease prevention and management. Overall, advances in this field have the potential to revolutionize nutritional guidance and impact improvements in metabolic-related outcomes.

Conflict of interest

The authors declare no conflict of interest.

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