Treatment of insulin resistance: straight from the gut

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Insulin resistance (IR) is a key pathological hallmark of obesity and type 2 diabetes. Emerging evidence has uncovered the gastrointestinal (GI) system as a previously overlooked player in fine-tuning systemic glucose homeostasis and insulin responses, which involved a complex inter-organ crosstalk through metabolic, endocrine, immune and neural mechanisms. These facts raise the intriguing possibility to explore the GI system as a new territory for IR intervention and glycemic control. Here we provide an overview of recent findings illustrating GI signals in the control of systemic insulin sensitivity and glucose homeostasis, and discuss the therapeutic prospects of exploiting the GI mechanisms to reverse IR and treat metabolic diseases.

Introduction

Metabolic disorders such as obesity and diabetes have reached the proportion of global epidemics. A well-established hallmark of the metabolic syndromes is insulin resistance (IR), which is also the driving force behind the metabolic syndromes. IR involves blunted insulin responsiveness from metabolic tissues including the liver, skeletal muscle and adipose tissue, and therapeutic strategies to restore insulin sensitivity have traditionally focused on these sites [1–3]. The causes of IR are certainly multifactorial, and accumulating evidence suggests that impaired insulin actions and deregulated glycemic control could implicate defects not restricted to the major metabolic tissues. Indeed, ever since the landmark finding of an altered gut microbiome in IR and associated metabolic syndrome nearly a decade ago [4], the intricate role of the gastrointestinal (GI) system in fine-tuning whole-body insulin sensitivity and metabolic health has been growing in appreciation. In recent years, remarkable progress has been made in understanding how GI signals are intricately associated with glucose homeostasis and disturbance at the systems level [5–11]. It is also somewhat unexpected to find that gut-derived actions are convincingly linked to the metabolic benefits of some pharmacological and GI surgical interventions [12–18]. These burgeoning yet enlightening findings place the GI tract within a more comprehensive network of IR pathology in metabolic diseases, which carries great implications for current efforts seeking treatment avenues.

The GI tract stands as a crucial interface of host interaction with external factors. Over the past decade, it has become clear that the GI system has evolved exquisite communications with distant organs to fine-tune host pathophysiology [19,20]. This inter-organ connection becomes disturbed in a number of metabolic diseases; therefore therapeutic interventions that address several defects in the regulatory system might be necessary. With novel targets increasingly identified from the gut for sensitizing insulin actions in states of health and disease, a picture emerges that gut-targeted therapeutics could be employed to strengthen the current arsenal of IR treatment. In this review, we aim to summarize key evidence showing that the GI tract is an underexplored player in the regulation of systemic insulin sensitivity and glucose homeostasis. We discuss how a gut-targeted pharmacological strategy could be designed to broaden the avenue of drug discovery for IR. We also consider the advantages as well as unsolved questions pertaining to the development and clinical translation of this attractive strategy.

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Evidence connecting the GI system with insulin responses

Gut microbiome and IR

The GI tract is the habitat of trillions of microbes collectively referred to as the gut microbiome, serving as a unique environmental factor in the regulation of host metabolism [21]. The observation of altered microbial composition in mouse models with metabolic syndrome was the early evidence drawing attention to the GI in IR [4]. This connection was later confirmed by the clinical report that microbial transfer from lean donors could augment insulin sensitivity in male recipients with metabolic syndrome [22]. Animal studies in the following years further linked GI dysbiosis with various adverse factors of insulin responses, such as metabolic endotoxemia and adipose tissue dysfunction [23]. In the meantime, the clinical significance of altered gut microbiome in the etiology of diabetes, obesity and cardiometabolic disorders has been increasingly appreciated [24,25]. More recently, the gut microbiome has also been uncovered as a previously neglected mediator in connecting the external factors (e.g., diet, drugs) with insulin responsiveness. For example, food additives such as artificial sweeteners were found to induce glucose intolerance and metabolic disturbance by altering the gut microbiome [26,27]. Also, the metabolic benefits of some IR-reversing medications and traditional medicines are partially linked to the modulation of the gut microbiome [16,28–30].

The implication of gut microbiome in IR is partially understood by some mechanistic links between microbial phenotypes and the immune and metabolic changes underlying IR [31]. As a typical example, butyrate, a microbial fermentation product from soluble fibers, exerts diverse effects on gut epithelial and immune cells, and circulates outside the GI to act on multiple insulin target tissues [32]. Not surprisingly, restoration of butyrate levels and/or butyrate-producing bacteria is consistently found to accompany the beneficial metabolic effects of gut-microbiome-based therapy in rodents and humans [22]. In fact, butyrate and other short-chain fatty acids (SCFAs; including acetate and propionate) have been proposed as specialized microbial metabolites that could mediate the microbial effects on the intestinal microenvironment and couple it with host health and disease [33]. Perturbation of the gut microbiome is therefore closely correlated with altered level and/or composition of the bioactive metabolites, which, via interaction with systemic receptors, trigger signals beyond the GI tract to regulate host metabolism and immunity [34].

GI mucosal system and IR

The GI mucosal system is a crucial player that orchestrates the bidirectional connection between the gut and systems organs. Among the putative pathways, endocrine signals participate in the physiological control of whole-body metabolism by inputs from the gut [35]. A well-known mediator from the intestine is glucagon-like peptide 1 (GLP-1), a signaling hormone that acts on multiple organs such as the liver and brain to regulate insulin sensitivity. The release of GLP-1 and other peptides (e.g., cholecystokinin, peptide YY) is coordinated by an array of molecular sensors distributed throughout the epithelial mucosa, which are potential targets for achieving remote control of insulin sensitivity. For example, intestinal farsenoid-X receptor (FXR) activation by bile acids triggers the release of GLP-1 and fibroblast growth factor 19 (FGF19) from intestinal L cells and ileocytes to communicate with systems organs [9]. In accordance, modulation of molecular sensors like FXR proved effective in controlling metabolism in distant organs. It was recently reported that inhibition of FXR signaling exclusively in the intestine with glycine-β-muricholic acid improved metabolic parameters and IR in obese mice [17]. Of interest, in a previous report, targeted intestinal FXR agonism by fexaramine in mice reduced systemic inflammation, hepatic glucose output and IR in high-fat diet (HFD)-induced obesity [36]. Despite the disparity in modulation, these findings illuminate a highly sophisticated sensory system in the gut to enable a powerful control of whole-body glucose homeostasis.

The mucosal sensory system plays an essential part in linking the gut microbiome with host insulin sensitivity and metabolic landscape. Specifically, in mice with HFD-induced obesity, specific disruption of intestinal epithelial Toll-like receptor (TLR) signals alters the gut microbiome composition, strengthens mucosal defense and improves glucose homeostasis [37]. Moreover, through the reciprocal relationship between gut microbiome and mucosal cells, the microbial changes are translated into altered immune and metabolic signals from the gut [38]. A notable example in this regard is the recent report that gut microbiome, through a direct metabolic signaling through SCFA and secondary bile acids (especially deoxycolate), promotes serotonin (5-hydroxytryptamine, 5-HT) biosynthesis from colonic enterochromaffin cells (ECs), which is the almost exclusive origin of peripheral 5-HT [39]. Such a microbiome–gut interaction might exert huge impacts on whole-body metabolism, in consideration with the previous finding that gut-derived 5-HT is a highly versatile signaling molecule that favors lipolysis and liver gluconeogenesis while preventing glucose uptake by hepatocytes [40]. More recently, circulating 5-HT was linked to the energy expenditure by the brown and beige adipose tissue. Of interest, genetic or pharmacological inhibition of gut 5-HT synthesis conferred protection in HFD-treated mice from obesity and IR, corroborating the therapeutic importance of gut 5-HT in metabolic control [8,41]. Clearly, these findings again indicate that the gut mucosal system should be viewed as a powerful modulator of gut-to-systems signals that powerfully insulin sensitivity and energy metabolism.

Enteric neural mechanisms and glucose homeostasis

Neural routes are important for the GI system to communicate with other organs in the control of whole-body metabolism. Typically, the vagal afferents in the GI relay the information of nutrient influx to the brain where a central sensory region exists to coordinate whole-body energy reserve and expenditure. Such a gut–brain crosstalk represents another machinery connecting environmental factors and systems glucose metabolism. For example, propionate from microbial fermentation of fructo-oligosaccharides, a kind of soluble fiber, was recently found to activate free fatty acid receptor 3 (FFAR3) in the periportal afferent neural system. This interaction initiates a gut–brain neural circuit that triggers intestinal gluconeogenesis to induce beneficial effects on glucose and energy homeostasis [6]. GI-derived apelin was also found to increase nitric oxide release in the brain via the enteric nervous system, which promotes glucose utilization in the muscle of normal and obese/diabetic mice [42]. Activation of this gut–brain–muscle axis was therefore a potential avenue to treat