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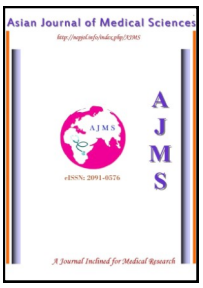
Upper intestine - New target for type-2 diabetes: A review



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Abstract

Type-2 diabetes is a chronic metabolic progressive disease, affects 200 million people worldwide will leads to increased death by more than 50% in the next 10 years. The ingested nutrients stimulate the release of gut peptides called incretins, which enhance the insulin secretion from pancreatic ß cell, in addition to this, recently, another gut mediated mechanisms called intestine-brain-liver axis to regulate glucose homeostasis by a neural circuit, initiated in the intestine in response to nutrient sensing, that increases sensitivity to insulin levels. In this mini review, the underlying mechanisms of gut related glucose regulation and its impact on the management of type-2 diabetes mellitus.

Key Words: Type-2 diabetes; Intestinal nutrients; Long chain fatty acids; intestine-brain-liver axis; metabolic surgery

1. Introduction

Since several thousand years ago, diabetes has remained a chronic progressive disease.[1] The disease now affects 200 million people worldwide, and diabetes-related death is expected to increase by >50% in the next 10 years.[2] The prevalence of diabetes among the elderly has increased 63% in the 10 years 1994-2004.[3] This increasing prevalence is a challenging to improvement in managing diabetes-related complications, as well as our global "modernization" and the accompanying metabolic derangements. Diabetes is now ranked as the sixth leading cause of death by disease in all over the world.[4] In many places, it ranks far higher. The economic burden in 2007 alone exceeded $174 billion.[5]

Modification of diet and oral hypoglycemic medications has proven inadequate, whereas insulin therapy only solves the problem temporarily. Consistent with the progressive nature of diabetes, monotherapy was abandoned in 75% of the patients studied in a follow-up of 9 years.[6] Even with the newest medication-therapies, patients continue to develop both the vascular complications. Diabetes is associated with increased cardiac- and stroke-related deaths, kidney failure, blindness, and 60% of nontrauma lower-limb amputations.[4] In cardiac surgery, diabetes as a preoperative risk factor confers greater morbidity than a previous myocardial infarction.[7,8] While these numbers show that diabetes will be the global health crisis of the next generation, its exact pathophysiology has yet to be delineated. Alternative treatments targeting different models of this disease require careful and responsible examination. A large number of evidence now demonstrates that intestinal lipids and incretins were produced in response to the transit of nutrients that boost insulin production from pancreatic beta cell.[9] "Upper intestine" is now emerging as an area dedicated to the establishment of management procedures specifically aimed at treating diabetes. This article will focus on the involvement of intestine-brain-liver axis as a new therapy for type 2 diabetes.

2.1. Food - neural circuit - insulin sensitivity

As the first point of contact with ingested food, the gastrointestinal tract is ideally positioned to initiate after-meal adaptations. Indeed, when nutrients are

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delivered into the gut, homeostatic mechanisms in place there are activated so that blood glucose levels are perturbed less than when nutrients are delivered directly into the blood. An established reason for this effect is that ingested nutrients stimulate the release of gut peptides called incretins, which enhance secretion of the hormone insulin, the main controller of blood glucose levels.[10] Wang *et al*[11] describe another gut-mediated mechanism that contributes to the regulation of glucose levels: a neural circuit, initiated in the intestine in response to nutrient sensing, that increases sensitivity to insulin.

2.2. Long chain fatty acids

Most adults consume 60–150 g/d of fat, containing mainly triglycerides (>90%). Digestion of triglycerides is initiated by lingual and gastric lipases, but is mainly controlled by pancreatic lipase in the proximal small intestine. Long-chain fatty acids (>12 carbon atoms) and monoacylglycerols derived from digestion of triglycerides bind to intestinal fatty acid–binding protein in enterocytes, are transported to the endoplasmic reticulum, and re-esterified into triglycerides. Cholesterol is esterified by cholesterol acyltransferase. Newly synthesized triglycerides and cholesterol esters are coated by phospholipids and apolipoproteins forming chylomicrons, which are delivered into the systemic circulation via the mesenteric lymphatics and thoracic duct. Thus, long-chain fatty acids reach muscle and adipose tissue through the systemic circulation before entering the liver. In contrast, medium-chain fatty acids (≤10 carbons) reach the liver directly via the portal vein. In addition to providing calories for storage and metabolism, dietary fat has profound effects on gastrointestinal function. Dietary fat slows gastric motility and emptying. Administration of lipids directly into the duodenum inhibits food intake in rodents and humans, likely through sensory vagal nerves from the gut to the nucleus of the solitary tract in the brain stem.[12] Recently, the importance of fatty acid metabolites as signals for regulation of feeding and glucose homeostasis has been highlighted.[13] Intestinal lipid infusions in Wang and colleagues' experiments specifically increased insulin sensitivity of the liver, reducing glucose output from this organ without affecting tissue glucose uptake. In unclamped rats, duodenal lipid infusions also contributed to glucose homeostasis, establishing the relevance of this mechanism to normal physiology.[11]

Intestinal lipids trigger these systemic effects due to formation of an LCFA metabolite called LCFA-CoA is sensed by the intestine. (The exact location and identity of the intestinal sensor cells are unknown.) They also showed that the link between lipid sensing in the gut and insulin action in the liver involves an intestine–brain –liver circuit within the parasympathetic nervous system, a subdivision of the peripheral nervous system. The LCFA-CoA signal passes from the gut, along the vagus nerve to the brain, through the hindbrain, and then back down vagal nerve branches that terminate in the liver (Fig-1). Wang and colleagues found that disruption of any component of this neural circuit eliminated the insulin-sensitizing effect of intestinal lipids, without affecting baseline glucose homeostasis.[11] So the intestine–brain–liver axis serves not as a basal regulator of insulin sensitivity but as a first responder to meals, preventing the circulating nutrient excess that would occur with profligate mobilization of internal fuel stores following a meal.

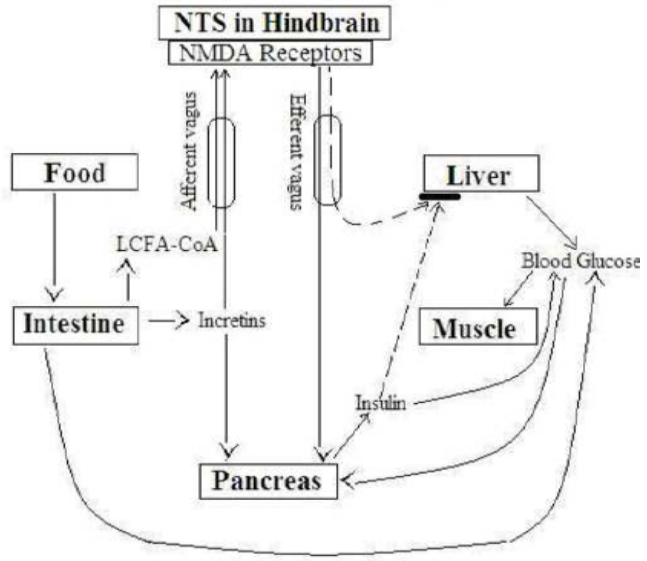

Figure-1: Intestine glucose homeostasis by intestine-brain-liver axis: Following a meal, lipid sensing in the intestine initiates processes that limit both of these sources through several mechanisms. Intestinal incretin peptides augment insulin secretion and also reduce food intake. Wang *et al*[11] demonstrated that LCFA-CoA molecules in the intestine activate an intestine–brain–liver neural circuit that enhances insulin sensitivity, suppressing glucose output by the liver. In the brain, LCFA-CoA, through NMDA receptors activate the vagal afferents leads to the stimulation of tract (NTS). The NTS will then send signals to the liver through the hepatic vagal afferent and suppress glucose.

A chronic surfeit of dietary fat can also reverse the beneficial effects of the acute lipid infusions Wang and colleagues studied. Long-term exposure to dietary lipids increases fatty-acid oxidation, lowering LCFA-CoA levels. Moreover, chronic fat intake causes insulin

resistance through weight gain and lipid accumulation in muscle cells. Lastly, compelling evidence indicates[14] that prolonged exposure to fatty acids from high-fat feeding and/or obesity stimulates inflammatory pathways that cause insulin resistance, perhaps overriding the acute insulin-sensitizing effects of intestinal lipids.

The revelation that intestinal nutrient sensing increases insulin sensitivity could aid our understanding of how bariatric surgery operations that promote weight loss by modifying the gastrointestinal tract ameliorates diabetes. A procedure known as Roux-en-Y gastric bypass surgery causes complete remission of diabetes in 84% of cases[15], and increasing evidence indicates[16] that this involves mechanisms beyond reductions in food intake and body weight. This operation, which alters the path of nutrients through the small intestine, increases the secretion of incretins. Wang and colleagues' work raises the untested possibility that complementary effects on the activity of the intestine–brain–liver neural circuit might further improve glucose metabolism.

2.3. Gut-brain-liver axis

The gut–brain and brain–liver axes exist to regulate energy and glucose homeostasis, respectively, W.C Grace *et al* has recently tested the existence of a lipid induced gut–brain–liver neuronal network in the regulation of glucose homeostasis.[11] First, they administered lipid to the duodenum, and a reduction of glucose production was observed. After establishing that upper intestinal lipids can regulate glucose homeostasis by suppressing glucose production, they examined the mechanisms involved. Co-infusions of lipids with triacsin C or tetracaine into the duodenum and vagal differentiation experiments were performed to demonstrate that the acute accumulation of the lipid metabolite in the duodenum, LCFA-CoA, is required to activate vagal signaling and suppress glucose production. By verifying that the vagus nerve plays a role in mediating the lipid-induced glucose production suppression effect, they investigated whether vagal signals from the intestine are sent to the nucleus of solitary tract (NTS). Upper intestinal lipids failed to suppress glucose production when they prevented the activation of N-methyl D-aspartate (NMDA) receptors in the NTS, providing evidence that NTS NMDA receptors are required for gut lipid-induced glucose production suppression effect. Lastly, a hepatic vagotomy was performed to demonstrate that upper intestinal lipid signals are relayed from the NTS to the liver via the hepatic vagal innervation. Altogether, these experiments support the existence of an upper intestinal lipid-induced gut–brain–liver neuronal axis (Fig.1), which represents one of the first lines of metabolic defenses against nutrient excess to provide metabolic balance by down-regulating glucose production on nutrient exposure. Various mechanisms remain to be elucidated to gain a complete understanding of how upper intestinal lipids regulate glucose homeostasis through the intestine–brain–liver neuronal network. Nonetheless, in combination with the previously mentioned gut–brain neuronal axis in the regulation of energy homeostasis, lipid-induced activations of the gut–brain and gut–brain–liver neuronal networks allow transient control of energy and glucose homeostasis upon the ingestion of lipids. One possible explanation for the inhibition of glucose responsiveness following exposure to high FFA levels could be modulation of KATP channel activity. It should also be noted that the molecular structure of the CoA moiety in the LCF-CoA molecule bears a very close resemblance to ADP, a known stimulator of the KATP channel.[17]

2.4. ATP sensitive K^+ channel

Insulin secretion from pancreatic ß-cells is essential in glucose homeostasis; it is regulated by many factors, including nutrients, hormones and neurotransmitters, among which glucose is physiologically the most important. The metabolism of glucose in pancreatic ß-cells is the crucial step in glucose-induced insulin secretion. Pancreatic ß-cells are electrically excitable cells and glucose regulates insulin secretion by controlling K+ permeability, which determines membrane potential.[18,19] Thus, the K+ permeability of the ß-cells is a critical determinant of glucose-induced insulin release. Before the identification of the ATP-sensitive K+ channels (KATP channels) in pancreatic ß-cells, however, the molecule linking glucose metabolism and membrane potential was not known. KATP channels were discovered originally in heart[20], and were later found in many other tissues including pancreatic ß-cells[21], skeletal muscle[22], smooth muscle[23], brain[24], pituitary[25] and kidney[26].

The activity of the KATP channels is controlled by intracellular ATP and ADP concentrations or the ATP/ ADP ratio. An increase in the ATP/ADP ratio closes the KATP channels (Fig-2), while a decrease in the ratio opens them. KATP channels play a regulatory role in

many cellular functions such as hormone secretion, excitability of neurons and muscles and cytoprotection in heart and brain ischemia, by linking the metabolic state of the cell to its membrane potential.[27]

The functional properties of KATP channels have been best characterized in pancreatic ß-cells[28]. Since the discovery of the KATP channels in ß-cells, the model in which glucose induced insulin secretion is dependent on the closure of the KATP channels has generally become accepted.[29]

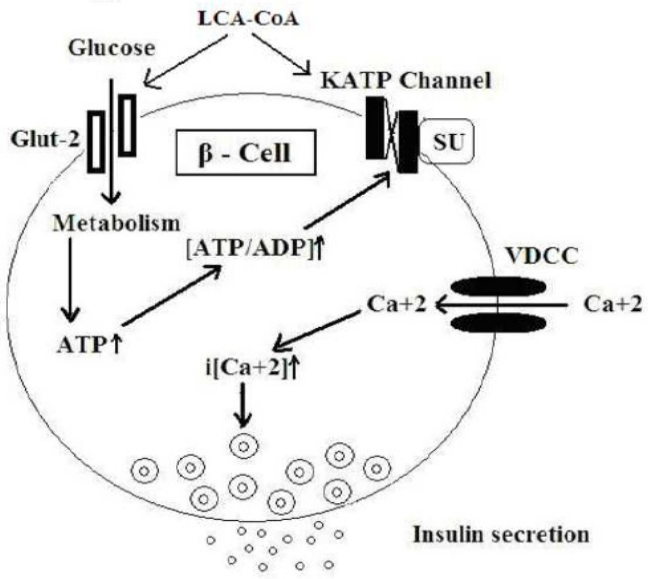

Figure-2. Activation of the KATP channel by LCA-CoA: (GLUT2, glucose transporter 2; VDCC, voltage-dependent calcium channel; SU, sulfonylurea). LCA-CoA can modulate the KATP channel and GLUT2 to increase in ATP/ADP ratio leads to closes the KATP channels, depolarizing the ß-cell membrane, leading to the opening of the voltage-dependent calcium channels, and allowing calcium influx. The rise in the intracellular calcium concentration ($[Ca^2+]i$) in the ß-cell then triggers insulin granule exocytosis

In this model, the increase in ATP/ADP ratio due to the metabolism of glucose closes the KATP channels, depolarizing the ß-cell membrane, leading to the opening of the voltage-dependent calcium channels, and allowing calcium influx. The rise in the intracellular calcium concentration ([Ca2+]i) in the ß-cell then triggers insulin granule exocytosis. Accordingly, the KATP channels, as ATP and ADP sensors, are thought to be critical in the regulation of glucose-induced insulin secretion. In addition, sulfonylureas such as tolbutamide and glibenclamide, widely used in the treatment of non-insulin-dependent diabetes mellitus, stimulate insulin release by closing the KATP channels directly.[30] Until recently, however, the molecular structure of the KATP channel was not known. During the past 3 years, molecular biological studies of KATP channels have provided insight into structure–function relationships, molecular regulation and pathophysiological role of the KATP channel.

2.5. Incretins

The ileal brake is a feedback phenomenon whereby ingested food activates distal-intestinal signals that inhibit proximal GI motility and gastric emptying.[31] It is mediated by neural mechanisms and several peptides that are also implicated in satiation. These engage a behavioral brake on eating to complement the ileal brake, restraining the rate of nutrient entry into the bloodstream.[32] One such peptide is glucagon-like peptide-1 (GLP1). It is cleaved from proglucagon, which is expressed in the gut, pancreas, and brain.[33] Other proglucagon products include glucagon (a counter-regulatory hormone), GLP2 (an intestinal growth factor), glicentin (a gastric acid inhibitor), and oxyntomodulin. Although several of these peptides are implicated in satiation, evidence is strongest for GLP1 and oxyntomodulin.

GLP1 is produced primarily by L cells in the distal small intestine and colon, where it colocalizes with oxyntomodulin and peptide YY (PYY). Ingested nutrients, especially fats and carbohydrates, stimulate GLP1 secretion by indirect, duodenally activated neurohumoral mechanisms, as well as by direct contact within the distal intestine.[34] The two equipotent bioactive forms, **$GLP1_{7-36}$** amide and **$GLP1_{7-37}$**, are rapidly inactivated in the circulation by dipeptidyl peptidase-4 (DPP4).[35] In addition to engaging the ileal brake, GLP1 accentuates glucose-dependent insulin release, inhibits glucagon secretion, and increases pancreatic ß cell growth.[33] Therefore, DPP4-resistant GLP1 congeners are being developed to treat diabetes.

GLP1 decreases food intake in several species[36], including humans[37]. Peripheral injections elicit satiety among normal-weight, obese, and diabetic[38] persons. Importantly, patients with diabetes treated with either GLP1 or the GLP1 receptor (GLP1R) agonist exenatide lose weight progressively in trials lasting up to two years.[39] This is especially remarkable because improved glycemic control achieved with other agents typically promotes weight gain.

The mechanisms underlying GLP1-induced anorexia are not fully known but involve vagal and possibly direct central pathways. Anorectic effects are mediated specifically by GLP1R, as they are absent in

GLP1R-deficient mice and are reversed with selective GLP1R antagonists.[40] GLP1R is expressed by the gut, pancreas, brainstem, hypothalamus, and vagal-afferent nerves.[33] The vagus is required for peripheral GLP1-induced anorexia, which is abolished by vagal transaction or differentiation.[41] Whether peripheral GLP1 also functions through central receptors is questionable. The peptide can cross the blood-brain barrier, but it seems unlikely that physiologically relevant quantities of endogenous peripheral GLP1 evade peripheral DPP4 degradation and penetrate the brain. However, GLP1 is produced by brainstem neurons that project to hindbrain and hypothalamic areas germane to energy homeostasis, possibly regulating appetite. Activation of hypothalamic GLP1R decreases food intake without causing illness, whereas GLP1R activation in the amygdala elicits malaise.[42] Although pharmacologic use of exenatide can stimulate the illness pathway, nausea is not the only mechanism reducing food intake. There is little correlation between the severity of nausea and the amount of weight lost, and doses of exenatide too low to cause nausea do promote weight loss.

Although GLP1 administration can reduce food intake, the physiologic importance of GLP1 in feeding was challenged by the observation that GLP1R-deficient mice have normal food intake and body weight.[43] Regardless of its physiologic significance in energy homeostasis, GLP1R overstimulation offers an attractive pharmacologic antiobesity strategy, because it reduces body weight while independently ameliorating diabetes.

3. Conclusion

The LCFA-CoA-stimulated intestine-brain-liver circuit through NMDA receptors in brain and KATP channel involvement in the release of insulin from β cells provides potential targets for novel antidiabetes drugs and a conceptual basis for antidiabetes diets. In the meantime, investigation into the pathophysiological basis of diabetes continues, with the hope of discovering the optimal therapeutic targets and best-suited interventions.

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